

CADTH Health Technology Review

Stereotactic Ablative Radiotherapy for the Treatment of Oligometastatic Cancer: A Clinical Review as Part of a Health Technology Assessment v1.0

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This is the baseline clinical review for a living systematic review. Please see the [CADTH project page](#) to access the latest version of the report and for the version history.

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Conflicts of Interest

There are no conflicts of interest to declare relevant to this report.

Abbreviations

3DCRT	3-dimensional conformal radiation therapy
ADT	androgen deprivation therapy
AE	adverse event
CI	confidence interval
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ENRT	elective nodal radiotherapy
GRIPP2-SF	Guidance for Reporting Involvement of Patients and the Public (version 2) – Short Form
HR	hazard ratio
HTA	Health Technology Assessment
IQR	interquartile range
LC	lesional control
LSR	living systematic review
OS	overall survival
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	quality of life
RCT	randomized controlled trial
RoB 2	Cochrane risk-of-bias tool for randomized trials
RoBANS	Risk of Bias Assessment Tool for Nonrandomized Studies
SABR	stereotactic ablative radiotherapy
SOC	standard of care

Table 1: Protocol Amendments

Section	Amendment	Page	Rationale
Decision problem	The decision problem was expanded beyond the elements related to the clinical review.	17	To reflect the scope of the entire Health Technology Assessment as described in the Scoping Brief. ¹
Research questions	The term “clinical effectiveness” replaced “clinical benefits” and the term “safety” replaced “clinical harms” in the phrasing of the 2 research questions.	18	To clarify the scope of information sought for each clinical research question.
Literature search methods	For the baseline review, the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) search portal was removed from the search strategy.	19	The access portal was not working when the baseline review was being conducted (March to August 2020).
Selection and eligibility criteria	The protocol stated that outcomes for question 2 are restricted to the AEs described in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For the baseline review and subsequent updates, all relevant studies reporting quantifiable AEs for both groups are included irrespective of the tools used.	21	To capture all AEs.
	The protocol stated that the progression-free survival and freedom-from-progression outcomes for question 1 included the time from randomization (or diagnosis for nonrandomized controlled trials) to any documented progression of disease at any site using RECIST. The lesional control outcome for question 1 was defined as time from randomization (or diagnosis for nonrandomized controlled trials) until radiological evidence of progression at the treated site or development of a previously unknown metastatic lesion using RECIST criteria. For the baseline review and subsequent updates, the restriction to the use of RECIST criteria for the definition of progression-free survival, freedom from progression, and lesional control outcomes is removed.	22	Progression-free survival and lesional control definitions varied among included studies and were not limited to RECIST criteria. No data were identified for the freedom-from-progression outcome for the baseline review; however, the protocol was amended to maintain a consistent approach for all progression-related outcomes for subsequent updates.
	The protocol defined lesional control as time from randomization (or diagnosis for nonrandomized controlled trials) until radiological evidence of progression at the treated site or development of a previously unknown metastatic lesion. For the baseline review and subsequent updates, lesional control was redefined as the absence of progression in the lesions initially present at randomization or at diagnosis from nonrandomized controlled trials.	22	Based on clinical expert input that lesional control only concerns existing lesions and not new lesions.

Section	Amendment	Page	Rationale
	<p>The protocol stated that studies of patients with a history of widespread metastatic disease (i.e., patients with induced oligometastatic cancer) would be excluded based on clinical expert input indicating that the nature of their disease progression is clinically different than the intended oligometastatic population for this review.</p> <p>The protocol also stated that for studies with mixed populations (i.e., comprising both individuals who met and those who did not meet the eligibility criteria) that did not report results for the population of interest separately, those studies would be considered eligible if at least 80% of the population met the inclusion criteria.</p> <p>For the baseline review and subsequent updates, it was clarified that “induced metastatic cancer” included “induced oligoprogression and induced oligopersistence.” In addition, results were included only if 100% of the population met the inclusion criteria.</p>	22	To clarify and ensure that the findings were relevant to the population of interest, based on further clinical expert input.
	<p>The protocol stated that if there were multiple publications fulfilling the inclusion criteria from the same study (i.e., same population), all publications that provided unique results (e.g., different outcomes or time points) would be included.</p> <p>For the baseline review and subsequent updates, all publications for each relevant study would be included, even if reporting the same results.</p>	23	For comprehensiveness, as there were no pre-specified criteria to determine which citation should be included when reporting results described in multiple publications.
Data extraction	<p>The protocol stated that Microsoft Excel and the SR management software DistillerSR² would be used to facilitate data extraction.</p> <p>For the baseline review, only Microsoft Excel was used for data extraction. This change will also be made for the updates.</p>	23	Microsoft Excel was sufficient for data extraction.
	<p>The protocol stated that data from each included study would be extracted by 1 reviewer and checked for accuracy by a second reviewer.</p> <p>For the baseline review, all relevant study data were extracted independently by 2 reviewers and then compared and combined. Discrepancies were resolved through discussion until consensus was reached, involving a third reviewer and clinical experts when necessary. This change will also be made for the updates.</p>	23	To further increase the methodological rigour.

Section	Amendment	Page	Rationale
Critical appraisal	<p>For the baseline review and subsequent updates, an overall risk-of-bias judgment was made for each nonrandomized study assessed with RoBANS, as follows:</p> <p>“high risk of bias,” if the study had at least 1 domain that was at “high risk of bias”</p> <p>“some concerns,” if the study had at least 1 domain that was “unclear” but no domain that was at “at high risk of bias”</p> <p>“low risk of bias,” if the study had a “low risk of bias” for all domains.</p> <p>This was not specified in the protocol.</p>	25	This was done to provide an overall risk-of-bias judgment for nonrandomized studies consistent with the planned approach to do this for RCTs. As the RoBANS guidance did not provide a specific approach for making study-level judgments, this was borrowed from the RoB 2 guidance for methodological consistency.
	<p>For the baseline review and subsequent updates, the risk of bias was assessed for individual outcomes within individual studies (i.e., bias due to deviations from missing outcome data and measurement of the outcome in RCTs, outcome assessment, and incomplete outcome data in nonrandomized studies). This was not specified in the protocol.</p>	25	To address sources of bias that may differ across outcomes within a single primary study.
Patient engagement	<p>The protocol stated that a patient will be invited to reflect on their personal experiences with SABR treatment prior to protocol finalization and during drafting and upon completion of the final report. This was updated to specify patient involvement during drafting and completion of the baseline clinical review, and to add opportunities for involvement during clinical review updates as part of the LSR phase and upon transitioning the clinical review out of living mode.</p>	27	To clarify the planned patient engagement activities for the baseline clinical review and throughout the LSR phase.

AE = adverse event; LSR = living systematic review; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumors; RoB 2 = Cochrane risk-of-bias tool for randomized trials; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; SABR = stereotactic ablative radiotherapy; SR = systematic review.

Table of Contents

Authors	3
Clinical Review	3
Patient Engagement	3
Research Information Science.....	3
Contributors.....	4
External Reviewer.....	4
Conflicts of Interest	4
Abbreviations	5
Summary	13
Key Messages	13
Abstract	13
Introduction	15
Background and Rationale	15
Decision Problem.....	17
Objective.....	17
Research Questions.....	18
Opportunities for Stakeholder Feedback.....	18
Methods	19
Study Design	19
Literature Search Methods	19
Selection and Eligibility Criteria.....	20
Study Selection	23
Data Extraction.....	23
Critical Appraisal.....	24
Data Analysis and Synthesis.....	25
Patient Engagement	26
Results	28
Quantity of Research Available	28
Study Characteristics.....	28
Critical Appraisal of Individual Studies.....	32
Data Analysis and Synthesis.....	37
Question 1: Clinical Effectiveness.....	38

Question 2: Safety.....	58
Patient Engagement	62
Summary of Results	63
Discussion	65
Generalizability of Findings	65
Limitations.....	66
Directions for Future Research	67
Conclusions and Implications for Decision-Making	69
References	70
Appendix 1: Analytical Framework	73
Appendix 2: Literature Search Methods	74
Appendix 3: PRISMA Flow Chart of Selected Reports.....	78
Appendix 4: List of Included Studies	79
Appendix 5: List of Excluded Studies and Reasons for Exclusion	80
Appendix 6: Considerations for Meta-Analyses	87
Appendix 7: Characteristics of Included Publications.....	88
Appendix 8: Critical Appraisal of Included Studies.....	99
Appendix 9: Main Study Findings	105

List of Tables

Table 1: Protocol Amendments.....	6
Table 2: Selection Criteria for Clinical Review	20
Table 3: Risk of Bias Summary – RCTs (Cochrane Risk of Bias Tool 250)	34
Table 4: Risk of Bias Summary – Nonrandomized Studies (RoBANS51,52)	36
Table 5: High-Level Summary of the Findings.....	37
Table 6: OS Comparing SABR With SOC Versus SOC	39
Table 7: PFS Comparing SABR With SOC Versus SOC	42
Table 8: Health-Related QoL Comparing SABR With SOC Versus SOC Alone.....	44
Table 9: Lesional Control Comparing SABR With SOC Versus SOC	45
Table 10: OS Comparing SABR Versus SOC.....	47
Table 11: PFS Comparing SABR Versus SOC.....	51
Table 12: Health-Related QoL Comparing SABR Versus SOC.....	55
Table 13: Lesional Control Comparing SABR Versus SOC	57
Table 14: Adverse Events Comparing SABR With SOC Versus SOC.....	59
Table 15: Adverse Events Comparing SABR Versus SOC.....	61
Table 16: Rationale for Not Conducting Meta-Analysis.....	87
Table 17: Characteristics of Included Primary Studies	88
Table 18: Risk of Bias Among Randomized Controlled Trials (Cochrane Risk of Bias Tool 250).....	99
Table 19: Risk of Bias Among Nonrandomized Studies (RoBANS51,52).....	102
Table 20: Overall Survival.....	105
Table 21: Progression-Free Survival	108
Table 22: Health-Related QoL.....	111
Table 23: Lesional Control.....	114
Table 24: Adverse Events	117
Table 25: Patient and Public Involvement in CADTH’s SABR for the Treatment of Oligometastatic Cancer HTA...	119

List of Figures

Figure 1: Analytical Framework.....	73
Figure 2: PRISMA Flow Chart of Selected Reports.....	78
Figure 3: Number of Included Publications by Publication Year	98

Summary

Key Messages

- Oligometastatic cancer (cancer with a limited number of metastases) represents an intermediate state between cancer confined to a single location in the body and cancer that has metastasized – or spread – widely.
- One treatment option, for which there is growing interest, is stereotactic ablative radiotherapy, also known as SABR.
 - SABR precisely delivers a high dose of radiation to ablate tumours at specific sites while minimizing the radiation dose to surrounding normal tissues.
 - SABR may be used independently or alongside other treatment options in the management of oligometastatic cancer.
- This CADTH clinical review evaluated the evidence regarding the clinical effectiveness and safety of SABR with or without standard of care (SOC) for people with oligometastatic cancer and found the following:
 - SABR in addition to SOC may offer a benefit in terms of overall survival (OS) and progression-free survival (PFS).
 - The findings for the effectiveness of SABR alone compared with SOC were mixed and deemed inconclusive.
 - There are insufficient data related to adverse events (AEs) at the present time to draw conclusions regarding the safety of SABR relative to SOC alternatives.
- Note that this is the baseline report of a living systematic review (LSR) that is being updated every 3 months to ensure the findings remain up-to-date as new evidence emerges. Please refer to the [CADTH project page](#) for the latest version of the report and for the version history.

Abstract

Context and Decision Problem(s)

Oligometastatic cancer (cancer with a limited number of metastases) represents an intermediate state between cancer confined to a single location in the body and cancer that has metastasized – or spread – widely. Treatment options for oligometastatic cancer may include surgery, conventional radiotherapy, or systemic therapy, depending on factors such as the type, location, and ease of access of each lesion. SABR is an additional treatment option for which there is growing interest. SABR precisely delivers a high dose of radiation to ablate tumours at specific sites while minimizing the radiation dose to surrounding normal tissues. SABR may be used independently or alongside other treatment options in the management of oligometastatic cancer.

While interest in the use of SABR for oligometastatic cancer is high, there remain key questions. What is the clinical effectiveness and safety of SABR for patients with oligometastatic cancer? What would form appropriate patient selection criteria and what would be the optimal dose or regimen? What is the cost-effectiveness of SABR, and what are the key implementation considerations? The purpose of this CADTH Health Technology Assessment (HTA) was to address these questions, starting with a review of the clinical evidence, which is presented here.

Clinical Effectiveness and Safety Evidence

Because the evidence on SABR for oligometastatic cancer is rapidly evolving, CADTH is using a "living systematic review" (LSR) format for the clinical review. The status of the LSR is being updated every 3 months to ensure the findings reflect the latest up-to-date evidence on the topic.

CADTH compared SABR plus SOC with SOC alone, and compared SABR alone with SOC alone, for people with oligometastatic cancer. Outcomes identified as important by patient and clinical expert input were OS, PFS, and AEs. Additional outcomes of interest included freedom from progression, health-related quality of life (QoL), lesional control (LC), and systemic therapy use after treatment.

A total of 3 randomized controlled trials (RCTs) and 6 nonrandomized studies were identified. The findings suggested there may be OS and PFS benefits associated with SABR plus SOC compared with SOC alone. However, the findings from the studies comparing SABR alone with SOC were mixed and deemed inconclusive. With regard to AEs, there are limited available data to assess whether SABR with or without SOC is more or less harmful than SOC alone. There was a lack of literature identified to inform conclusions for other outcomes of interest.

Conclusions and Implications for Decision- or Policy-Making

The current clinical evidence suggests that SABR plus SOC may offer survival benefits for patients with oligometastatic cancer. To inform patient selection criteria, future research on the effectiveness of SABR in patients with different characteristics would clarify who might benefit most from this treatment. Evidence on the optimal regimen or dose of SABR for the treatment of oligometastases is also needed. Additional studies are expected to be identified during the LSR phase of this project. Finally, this clinical review represents 1 component among many that decision-makers will consider when making the decision about the expanded use of SABR in Canada. CADTH is currently undertaking an Environmental Scan of implementation considerations that will contribute to this HTA to further support decision-making.

Introduction

Background and Rationale

Cancer and Oligometastatic State

Cancer is the leading cause of death in Canada, comprising 30% of all death events.³ In 2020, there will be an estimated 225,800 new cancer cases and 83,300 deaths.³ Tumour metastasis is the main cause of cancer-related death.^{4,6} The development of metastases is a potential complication among patients with cancer.⁷ Metastasis occurs when cancer cells, originating from 1 part of the body, move from the place of origin (primary tumour) and spread to another location to form 1 or more tumours.^{4,7} The extent of systemic disease and the number, size, and location(s) of lesions can affect the overall prognosis for a patient.⁸

In 1995, Hellman and Weichselbaum first introduced the term oligometastatic state and proposed that the process of cancer metastasis occurs along a continuum — from localized to widespread metastatic disease.^{9,10} Oligometastases may represent a paradigm shift in the treatment intent for metastatic cancer: if a limited number of metastases can be treated, then the outcome may be curative.¹¹ Hellman and Weichselbaum described 2 different clinical scenarios that would both be considered oligometastases “tumours early in the chain of progression with metastases limited in number and location,” and “patients with oligometastases who had widespread metastases that were mostly eradicated by systemic drugs, the chemotherapy having failed to destroy those remaining because of the number of tumour cells, the presence of drug-resistant cells, or the tumour foci being located in some pharmacologically privileged site.”⁹ Moreover, as these 2 classes of oligometastases represent different clinical scenarios, they are associated with different prognoses and may also require different treatments.¹² Current definitions of oligometastatic disease in the literature are heterogeneous, although the European and American societies for radiotherapy and oncology recently published a consensus definition as 1 to 5 metastatic lesions, with control of the primary tumour being optional but where all metastatic sites must be safely treatable.¹³

Since the publication of this seminal paper by Hellman and Weichselbaum,⁹ the concept of oligometastasis has been generally accepted; however, specific criteria that define an oligometastatic state, such as the number of metastases and organ sites, are still unclear.^{12,14} Oligometastasis includes situations where the primary tumour is present, not present (i.e., removed), treated, or untreated; therefore, a patient can have oligometastases regardless of the state of the primary tumour.¹⁵ Moreover, patients can be described as having synchronous oligometastatic disease (maximum 6-month interval between the diagnosis of oligometastatic disease and the primary cancer diagnosis) and metachronous oligometastatic disease (more than a 6-month interval between the diagnosis of oligometastatic disease and the primary cancer diagnosis).¹² Imaging is currently the most relevant diagnostic method for defining oligometastatic cancer, which is broadly understood as a limited number of metastatic lesions.^{12,16}

Stereotactic Ablative Radiotherapy

Treatment options for patients presenting with oligometastatic cancer may include, but are not limited to, surgery, conventional radiotherapy, systemic therapy (e.g., chemotherapy, hormone therapy), observation, and ablative therapies such as cryoablation, microwave ablation, radiofrequency ablation, and SABR.^{11,17-19} SOC is variable according to the type of cancer. The notion of using targeted therapies such as surgery or radiation therapy to eliminate oligometastatic disease has been termed metastasis-directed therapy or local

consolidative therapy.^{9,20,21} Metastasis-directed therapy has been shown to improve survival relative to SOC (observation or maintenance systemic therapy) in RCTs of patients with oligometastatic prostate cancer²² and non-small cell lung cancer.²¹ In those studies, the choice of surgery or radiation therapy, particularly SABR, was determined by the multidisciplinary team and patient characteristics. Though there are multiple treatment options within the class of metastasis-directed therapies, and surgical resection is considered the gold standard for the treatment of certain oligometastases (e.g., partial liver resection for metastases from colorectal cancer), SABR may be an alternative non-invasive treatment option for achieving LC.¹⁷

SABR, also known as stereotactic body radiation therapy (SBRT), is a method of precisely delivering high doses of radiation to ablate tumours at specific sites while sparing radiation dose to surrounding normal tissue.²³⁻²⁵ First developed in Sweden in the early 1990s,²⁶ SABR builds on the treatment delivery paradigm used to treat brain tumours with intracranial stereotactic radiosurgery, but it targets tumours outside of the brain (e.g., lungs, liver, bone, and lymph nodes).²³ SABR relies on an imaging component to map the treatment area using computerized tomography (CT) scans or magnetic resonance imaging (MRI), tumour motion reduction, and reproducible patient set-up strategies (e.g., respiratory compression, body immobilization devices [e.g., alpha-cradle or vacuum-lock system]), and advanced radiotherapy-delivery techniques using conventional linear accelerators or novel precision delivery systems.²³ Newer technology with the potential for application in this area includes C-arm S-band linear accelerator systems, robotic X-band CyberKnife, image-guided Gamma Knife Icon system, proton-based applications, and MR Linac.^{27,28} SABR is considered an alternative to surgical resection and is often the preferred option for patients with cancer that is medically inoperable. Treatment advantages include limited recovery time before resuming systemic therapy and the ability to treat areas with metastatic involvement that are either not surgically accessible or include more than 1 organ, or patients at high risk of post-operative complications.¹²

SABR in Canada

The availability of SABR has increased across Canada. In 2014, a survey of 41 Canadian radiotherapy centres reported that 5 provinces (British Columbia, Alberta, Manitoba, Ontario, Quebec) had centres with SABR capacity and substantial growth was expected.²⁹ Currently, all provinces in Canada have SABR capability.³⁰ SABR is also available in some northern centres (e.g., Northeast Cancer Centre in Ontario).³¹ Canadian centres are using SABR to treat primary tumours and oligometastases in different areas of the body, such as the lungs, liver, bone, and lymph nodes.^{29,32} However, there is variation in patient selection criteria for SABR treatment across radiotherapy centres, and not all centres offer SABR for the treatment of oligometastases.²⁹

CADTH received input from Canadian jurisdictions that identified several common considerations regarding the use and implementation of SABR for oligometastatic cancer. There is a desire to determine the appropriate use of SABR across Canada regarding which patients should be treated with SABR in order to achieve the greatest benefit (e.g., location and number of metastases) and how those patients should be managed (e.g., radiation dose fractionation, treatment sites, immobilization methods, tumour-tracking methods, and image guidance strategies). Decision-makers are also seeking more information regarding the long-term outcomes of treatment with SABR. In addition to patient treatment and management, jurisdictions expressed interest in gathering information regarding the implementation of the technology, including how other jurisdictions have successfully operationalized the use of technology for oligometastatic cancer (e.g., billing codes, time to treatment, length

of individual treatment sessions, staffing), and in a review of resource and infrastructure considerations (e.g., requirements for additional staff training, software, or equipment upgrades). An understanding of patients' and clinicians' perspectives (e.g., acceptability, feasibility) and ethical considerations (e.g., a shifting risk-benefit profile compared with standard care) will also become salient if expanded use of SABR is pursued. Equity issues relating to accessing SABR as a result of the specialized nature of therapy and its delivery in urban centres may also emerge. All of the jurisdictions that responded expressed an interest in an economic analysis of the expanded use of this technology.

Moreover, the use of SABR for the ablation of oligometastases is an active area of research. Specifically, a 2019 paper identified 64 ongoing studies examining SABR for oligometastatic cancer.³³ In the summer of 2016, the National Health Service (UK) produced a policy document stating that it would not routinely commission SABR for oligometastatic cancer, given there was inconclusive evidence to support the provision of treatment.³⁴ However, recently identified evidence has suggested the potential for improved health outcomes, such as OS and PFS, with the use of SABR for oligometastases.³⁵ A CADTH HTA is warranted for critically reviewing the current evidence of SABR in the treatment of patients with oligometastatic cancer.

Decision Problem

Based on the context, jurisdictional feedback, and results of a detailed scoping exercise, the aim of a CADTH HTA on this topic was to inform the following decision problem:

- Should the use of SABR be expanded to include the treatment of patients with oligometastatic cancer?
 - If so, what are the appropriate patient selection criteria?
 - If so, what is the optimal regimen or dose?
- What is the value for money and affordability of SABR for oligometastatic cancers?
- What are the main challenges to and enablers of the implementation of SABR in Canada?

Objective

The clinical evidence regarding SABR is still developing; therefore, a staged approach to this HTA was followed, as proposed in the Scoping Brief.¹ CADTH first conducted a clinical review using systematic review methods to synthesize and critically appraise the current evidence of SABR for the treatment of patients with oligometastatic cancer. An Environmental Scan is also being conducted to explore considerations for the implementation of SABR for this purpose.

The scoping review did not identify any qualitative literature on the topics of oligometastatic cancer or SABR. Given the paucity of published evidence, engaging directly with patients who have experience with SABR is a more relevant method for capturing patients' experiences with this health technology.

Similarly, the scoping review did not identify any literature reporting ethical considerations related to the use of SABR for the treatment of oligometastatic cancer. Ethical considerations were acknowledged and discussed among the broader review team, such as the potential to exacerbate existing equity considerations regarding access to cancer treatments, and the aforementioned challenges in defining an oligometastatic state. However, in consultation with

ethics experts and in the absence of published literature, it was determined that a full ethical analysis would not be warranted.

As previously noted, jurisdictions have expressed an interest in an economic analysis of the expanded use of SABR for oligometastatic cancer. At the time of the protocol development in 2020, CADTH was aware of several Canadian groups conducting analyses addressing the economic considerations regarding the use of SABR for the treatment of oligometastatic cancer. To avoid duplication of effort, CADTH will monitor ongoing Canadian economic analyses and attempt to broker existing work to meet the economic evidence needs of stakeholders.

The objective of this report is to address the decision problem by assessing the clinical effectiveness and safety of SABR in the treatment of patients with oligometastatic cancer through a systematic review of the literature. As the clinical evidence regarding SABR is still developing and there are several ongoing clinical trials, CADTH will use an LSR approach to regularly update the review. The deliverable for this report is the baseline review of an LSR of the clinical evidence. The results of the Environmental Scan will be incorporated in the report upon subsequent updates to this review. An analytical framework (Figure 1) guiding the clinical review can be found in Appendix 1.

Research Questions

This clinical review addressed the following research questions:

1. What is the clinical effectiveness of SABR alone or in combination with other therapies for the treatment of patients, of any age, with oligometastatic cancer?
2. What is the safety of SABR alone or in combination with other therapies for the treatment of patients, of any age, with oligometastatic cancer?

Opportunities for Stakeholder Feedback

Stakeholders (i.e., clinicians, policy-makers, researchers, health associations) have been given the opportunity to provide feedback on the draft of the list of included studies and a draft report of the baseline clinical review. No unpublished data were identified as part of the feedback process. Additionally, CADTH will periodically (e.g., annually) seek input from decision-makers in Canadian jurisdictions to determine whether there is continued interest in this topic to inform whether to maintain or transition the review out of living mode.

Methods

The conduct of the clinical review was informed by a CADTH Rapid Response report,³⁶ an informal scoping review of the existing literature (Scoping Brief),¹ discussion with clinical experts, and patient engagement. A protocol³⁷ was written a priori, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols (PRISMA-P)³⁸ for guidance on clarity, transparency, and completeness, and the protocol was followed throughout the study process. Any deviations from the prospectively registered protocol were disclosed in the final report (Table 1: Protocol Amendments) and updates were made to the PROSPERO submission accordingly (registration number: CRD42020167767).

Study Design

This clinical review was designed as an LSR to answer research questions 1 and 2, enabling continual surveillance and updates to the analysis contingent on following a priori stopping rules (see Project Protocol³⁷ for more details). The LSR model will allow for ongoing assessment of the clinical effectiveness and safety of SABR, and the incorporation of the results from several ongoing clinical trials identified during the scoping process with expected completion dates ranging from the year 2020 through 2029 as well as the results of any other relevant trials or studies that may be currently under way.

This review aims to comprehensively explore the clinical effectiveness and safety of SABR for oligometastatic cancer for different primary tumours and any metastatic sites amenable to SABR, as outlined in research questions 1 and 2. Specifically, CADTH decided to conduct an LSR in consideration of the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.³⁹

This report presents the baseline review for the LSR, which is in keeping with the same core methods and review steps as a standard systematic review. Thus, standard systematic review methods (e.g., screening, data extraction, risk-of-bias assessment) were followed. The clinical review is now considered in living mode with the publication of this baseline review. Details on the updating and ending of the LSR can be found in the protocol.³⁷

Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (www.cadth.ca/resources/finding-evidence/press).⁴⁰ The complete search strategy is presented in Appendix 2.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were SABR and oligometastatic cancer. The following clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, the Health Canada Clinical Trials Database, and the Canadian Cancer Trials Database.

No filters were applied to limit the retrieval by study type. Retrieval was limited to publications published between January 1, 1990 and March 20, 2020. Conference abstracts were excluded

from the search results, though they were reviewed by clinical team members for forecasting purposes.

The initial search was completed on March 20, 2020. Monthly alerts were conducted until the end of the stakeholder feedback period for the baseline review (January 18, 2021). Since then, alerts are run every 3 months to support the LSR phase of the HTA. The clinical trial registries search was updated prior to the completion of the stakeholder feedback period for the baseline review. Following the completion of the baseline report, the clinical trial registries search will be updated every 6 months.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool for Searching Health-Related Grey Literature checklist (www.cadth.ca/grey-matters),⁴¹ which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented through contacts with experts, as appropriate. The grey literature search was updated prior to the completion of the stakeholder feedback period. Grey literature will be updated every 6 months during the LSR phase of the HTA. See Appendix 2 for more information on the grey literature search strategy.

Selection and Eligibility Criteria

Studies were included if they met the eligibility criteria, including the specific population, intervention, comparators, and outcomes (PICO), presented in Table 2. The inclusion criteria were informed by the CADTH Rapid Response report,³⁶ the informal scoping review of the existing literature,¹ patient engagement, and consultation with clinical experts.

Table 2: Selection Criteria for Clinical Review

Population
<p>Patients with oligometastatic cancer (i.e., limited metastatic lesions). No restrictions on age, sex, gender, ethnicity, comorbidities, location of primary cancer site, or length of time since diagnosed.</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Patients with metastases in the brain only • Patients with a previous history of widespread metastatic disease
Intervention(s)
<p>SABR of any dose or fractionation alone or in combination with 1 or more concurrent or neoadjuvant therapies, for example:</p> <ul style="list-style-type: none"> • surgery • conventional radiotherapy • chemotherapy • immunotherapy • hormone therapy • other ablative treatments, such as cryoablation and radiofrequency ablation • targeted therapy (e.g., targeting specific mutations, proteins) • standard of care (not otherwise specified)

Comparator(s)
Standard of care (variable according to cancer type). For example: <ul style="list-style-type: none"> • surgery • conventional radiotherapy • chemotherapy • immunotherapy • hormone therapy • other ablative treatments, such as cryoablation and radiofrequency ablation • targeted therapy (e.g., targeting specific mutations, proteins) • no treatment
Outcomes
Question 1 (clinical effectiveness): <ul style="list-style-type: none"> • OS^{a,b} • PFS^{a,c} • freedom from progression^d • health-related quality of life^{a,e} • LC^f • systemic therapy use (e.g., yes or no; number of cycles of chemotherapy and systemic therapy; total duration of the chemotherapy and systemic therapy) Question 2 (safety): <ul style="list-style-type: none"> • adverse events
Study design(s)
Comparative study designs: <ul style="list-style-type: none"> • randomized controlled trials • nonrandomized controlled trials^g • cohort studies^h • case-control studies Exclusions: <ul style="list-style-type: none"> • cross-sectional studies • single-arm before-and-after studies or single-arm interrupted time series studies • case reports • case series • qualitative studies • guidelines • review articles • editorials, letters, and commentaries • studies of any design published as conference abstracts, presentations, or dissertations
Study setting
Any setting
Time frame
1990 to present ⁱ
Language
Studies published in English

AE = adverse event; LC = lesional control; OS = overall survival; PFS = progression-free survival; SABR = stereotactic ablative radiotherapy.

^a These outcomes were identified as being of importance to a patient, based on the input received during an interview conducted by CADTH.

^b OS: Time from randomization (or diagnosis for nonrandomized controlled trials) to death from any cause. OS is appropriate for this review, as it is generally based on objective and quantitative assessment.

^c PFS: Time from randomization (or diagnosis for nonrandomized controlled trials) to any documented progression of disease at any site, appearance of new metastases, or death from any cause, whichever occurs first (follow-up: any length of time).

^d Freedom from progression: Time from randomization (or diagnosis for nonrandomized controlled trials) to any documented progression of disease at any site or appearance of new metastases, whichever occurs first (follow-up: any length of time).

^e Health-related quality of life. All instruments measuring quality of life were considered; possible questionnaires included: Functional Assessment of Cancer Therapy–General (FACT-G), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), MD Anderson Symptom Inventory for Lung Cancer (MDASI-LC).

^f LC: The absence of progression in the lesions initially present at randomization (or at diagnosis for nonrandomized controlled trials).

^g Nonrandomized controlled trials are defined as a clinical trial in which the participants are not assigned by chance to different treatment groups. Participants may choose which group they want to be in, or they may be assigned to the groups by the researchers.⁴²

^h Cohort studies are defined as studies in which participants are sampled based on exposure and in which outcomes are assessed in a follow-up. This is distinct from case series studies, in which participants are sampled based on the presence of an outcome, or of both an exposure and outcome, where absolute or relative risk cannot be calculated.⁴³ Only study designs providing comparative evidence are eligible for inclusion.

ⁱ SABR was first developed in the early 1990s in Sweden,²⁶ and the term oligometastatic state was first introduced by Hellman and Weichselbaum in 1995.⁹ Given this, only studies published after the year 1990 were included, which should include a complete list of relevant studies.

For this clinical review, the population of interest was patients with oligometastatic cancer, described by study authors as having limited metastatic lesions using terminology such as “oligo,” “limited,” or “few.” Studies that did not state clearly that the patient population was restricted to or included oligometastatic patients were excluded. Oligometastasis includes situations where the primary tumour is present, not present (i.e., removed), treated, or untreated.¹⁵ Since a participant can have oligometastases regardless of the state of the primary tumour, the status of the primary tumour was not part of the eligibility criteria.¹⁵ Moreover, this review included patients with an imaging-based diagnosis of a limited number of metastases identified at presentation or prior to initial therapy, or a limited number of metastases identified after initial therapy of the primary tumour, or a metastatic relapse of a limited number of metastases where initial metastatic sites are controlled or resolved, or a known metastatic site that responded to previous treatment (local treatment or systemic treatment or both) that showed interval growth (or regrowth) with or without a systemic-free interval.^{12,44-47} Studies of patients with a history of widespread metastatic disease (i.e., patients with induced oligometastatic cancer, including induced oligoprogression and induced oligopersistence) were excluded based on clinical expert input indicating that the nature of their disease progression is clinically different than the intended oligometastatic population for this review.¹² Studies that included patients with a history of metastases but did not report enough detail to determine whether this represents a history of oligometastasis (i.e., limited or few metastases) versus a history of widespread metastatic disease were also excluded. Studies with mixed populations (i.e., comprising both individuals who met and those who did not meet the eligibility criteria) were considered eligible for inclusion if the results pertaining to the population of interest were reported separately.

The intervention of interest was SABR (synonym: SBRT), with or without 1 or more concurrent or neoadjuvant therapies. Stereotactic radiosurgery for brain-only metastases was excluded, as ablative therapy to the central nervous system is more clinically established and not the focal area of interest for this HTA.⁴⁸ Studies of metastasis-directed therapy that did not report results specific to SABR were also excluded. For instances where the intervention was SABR in combination with 1 or more concurrent or neoadjuvant therapies, the study was eligible for inclusion if the comparator also included the same concurrent or neoadjuvant therapies in order to explore the true effects of SABR.

For the clinical effectiveness outcomes for research question 1, the data at all time points as reported in the included studies were included, but different time points were not combined. In cases where studies used more than 1 tool to assess health-related QoL, all data were included. The “systemic therapy use” outcomes were meant to explore whether there was a difference in the need for systemic therapy subsequent to treatment with SABR (e.g., in terms of the number of cycles or total duration of systemic therapy) compared with the use of systemic therapy in patients who do not receive SABR.

For the safety outcomes for research question 2, data that allowed for comparisons between the intervention and comparator groups were of interest and included, irrespective of the tools used to measure or describe the AEs (e.g., frequencies or prevalence of individual or grades of AEs [e.g., grades 1 to 2 versus grades 3 to 5] reported for each group were in scope, but non-quantifiable lists of AEs for both groups were not in scope).

If there were multiple publications fulfilling the inclusion criteria from the same study (i.e., same population), all publications were included; in those cases, data from multiple publications were extracted and discussed as 1 single study.

Study Selection

Study selection was conducted using the systematic review management software DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers independently screened titles and abstracts of all retrieved citations (i.e., literature searches of academic databases, clinical trial registries, grey literature searches, citations identified by clinical content experts, and stakeholder feedback) against the eligibility criteria (Table 2). Exclusion by both reviewers was required for a record to be excluded at the title and abstract level. Articles that were judged to be potentially relevant by at least 1 reviewer from their title or abstract were retrieved for full-text screening. The same 2 reviewers independently examined all full-text articles against the eligibility criteria and compared their included and excluded studies from the full-text review. Consensus was required for inclusion in the review. Discrepancies were resolved by discussion between the 2 reviewers, through the involvement of a third reviewer, or by consultation with a clinical expert as needed.

Studies identified via monthly database search alerts and semi-annual clinical trial registry and grey literature search alerts meeting the selection criteria of the review were incorporated into the analysis if they were identified before the end of the stakeholder feedback period for this baseline review. Since the stakeholder feedback period, database search alerts have been scheduled every 3 months, and clinical registry and grey literature search alerts will continue on a semi-annual basis, as part of the LSR protocol. Any studies identified after the stakeholder feedback period will be retained to be screened along with the next set of results from database search alerts (conducted every 3 months as part of the LSR process).

Lists of included studies and excluded studies were generated. The study selection process was documented in a PRISMA⁴⁹ flow chart (Appendix 3).

Data Extraction

Reviewers used Microsoft Excel to document and tabulate all relevant information from the included studies. Using the data-extraction spreadsheet, 2 reviewers extracted data independently and then compared and combined their data. Discrepancies were resolved through discussion until consensus was reached; when necessary, a third reviewer or clinical experts were also involved.

The following relevant information was extracted, where available:

- Study level: Description of publication (e.g., first author's last name, title, publication year, journal), study characteristics (e.g., clinical trial registry identification number, trial acronym, objectives, study design, year of the conducted study, sample size, study setting, country of the conducted study, study funding source).
- Patient level: Number of patients, age (mean, standard deviation), proportion of women or female patients (as reported by study authors), clinical situation of the diagnosis (e.g., limited metastases at presentation or prior to initial therapy, after therapy, relapse), number of metastases (mean, standard deviation), location of primary tumour site, status of primary tumour (e.g., treated versus untreated), previous treatment (e.g., for the primary tumour or for metastases), location(s) of metastases, number of metastases per metastatic site.
- Intervention level: Type (SABR, co-intervention), dose, total duration of treatment, frequency of treatment (e.g., single dose, multiple fractions or treatment), equipment type (brand).
- Comparator level: Type (e.g., surgery, conventional radiotherapy, chemotherapy, immunotherapy, hormone therapy, other ablative treatment [cryoablation, radiofrequency ablation, and so forth], targeted therapy [e.g., targeting specific mutations, proteins], no treatment), dose, total duration of treatment, frequency of treatment (i.e., number of cycles), and equipment type (brand).
- Outcome level: Description of outcomes (e.g., subgroup definition, measurement method, unit of measurement, length of follow-up), results, and conclusions of outcomes and subgroups of interest.

Data were extracted for all relevant outcomes for this study at any duration of follow-up. Measures of treatment effects (e.g., risk ratios, odds ratios, or risk differences for dichotomous outcomes, mean differences or standardized mean differences for continuous outcomes, and hazard ratios [HRs] for survival outcomes), and any results of statistical tests reported on those measures were extracted. Data from figures were extracted if explicit numerical data were reported. No attempts were made to contact study authors, as no relevant data were deemed conflicting or missing and needed for meta-analyses, which were the 2 conditions pre-specified in the protocol for contacting the corresponding authors.³⁷

As mentioned, if a study was reported in multiple publications and each publication provided unique results, data from these publications were extracted and discussed as 1 single study.

Critical Appraisal

The risk of bias of the primary studies was systematically evaluated using the methods described in version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2)⁵⁰ and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS),^{51,52} including cohort studies.

The RoB 2 tool⁵⁰ allowed for the assessment of 5 sources of bias or “domains”: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each question within each domain was answered with a yes, probably yes, probably no, no, or no information. Afterwards, a judgment of “low risk of bias,” “high risk of bias,” or “some concerns” was assigned for each domain, with rationale for each decision included in the comments box field.⁵⁰ An overall risk-of-bias judgment for each study was

provided as “high risk of bias” if the study had at least 1 domain that was at “high risk of bias;” “some concerns” if the study had at least 1 domain that indicated “some concerns” but no domain that was at “high risk of bias;” or “low risk of bias” where the study had “low risk of bias” for all domains, as per the RoB guidance.⁵⁰

The RoBANS tool^{51,52} allowed for the assessment of the risk of 5 types of bias across 8 domains: the possibility of the target group comparisons, target group selection, confounder, exposure measurement, blinding of assessors, outcome assessment, incomplete outcome data, and selective outcome reporting. For each item, a risk-of-bias judgment of “low,” “high,” or “unclear” was assigned with rationale for each decision included in the comments box field.⁵¹ An overall risk-of-bias judgment for each study was provided as “high risk of bias,” where the study had at least 1 domain that was at “high risk of bias;” “some concerns,” where the study had at least 1 domain that was “unclear” but no domain that was at “at high risk of bias;” or “low risk of bias;” where the study had “low risk of bias” for all domains. As the RoBANS guidance did not provide a specific approach for making study-level judgments, this was borrowed from the RoB 2 guidance for methodological consistency.

For sources of bias that may differ across outcomes within a single primary study (i.e., bias due to deviations from missing outcome data and measurement of the outcome in RCTs; outcome assessment and incomplete outcome data in nonrandomized studies), the risk of bias was assessed for individual outcomes within individual studies.

The risk-of-bias assessments of the included studies was performed by 1 reviewer and verified by a second reviewer. All disagreements were resolved through discussion between the 2 reviewers. The tools were used as a guide to evaluate the risk of bias in the included studies; additional insight beyond the items on the instruments has also been provided, when applicable. Summary scores were not calculated; rather, the strengths and limitations of each included study and how they affect the study findings were described narratively. Results of the risk-of-bias assessment were not used to exclude studies from this review.

Data Analysis and Synthesis

Narrative Synthesis

Narrative syntheses were performed. The narrative syntheses included presentation of study characteristics (e.g., the total number of studies included, study designs, publication years, countries in which the studies were conducted, and PICO elements, including dose) and findings within the main text and summary tables. All data analyses and narrative syntheses for this review were conducted separately for each outcome. Under each outcome, all intervention-comparator comparisons were grouped under 1 of 2 different categories — SABR plus SOC versus SOC alone and SABR alone versus SOC alone — which allowed us to summarize the effects of SABR alone or in combination with 1 or more concurrent therapies separately.

For assessing safety outcomes (research question 2), AEs were reported as described in each respective publication. In some studies, the number of patients experiencing an AE or complication was reported, whereas in other studies, the number of unique AEs or complications (i.e., events) was reported; in both cases, some individuals may have experienced more than 1 AE or complication.

The direction and size of any observed effects and any results of statistical tests that reported on those effects were summarized across studies, including an assessment of the likelihood of

clinical benefit (i.e., research question 1, clinical effectiveness) or harm (i.e., research question 2, safety). If relevant statistical comparisons were not conducted in the primary studies, this was explicitly stated; the direction of findings was summarized subjectively where possible in the text (e.g., whether the outcome variable changed numerically over time or was numerically different between groups) and overall findings were described as “uncertain” or “unclear.”

The following subgroups were of interest for both narrative and quantitative syntheses for research question 1:

- age
- sex or gender
- location of primary tumour site
- number of metastases sites (e.g., number of metastatic locations; single [e.g., lung only] versus multiple sites [e.g., lung, kidney, adrenal])
- number of metastases (e.g., total, regardless of metastatic location; 5 or fewer versus 3 or fewer metastases)
- location of metastases (e.g., metastatic site specific [e.g., prostate only, lung only])
- previous treatment of primary tumour (i.e., yes, no)
- previous treatment of metastases (i.e., yes, no).

Any relevant data on these subgroups of interest were extracted and analyzed.

A narrative summary of the results of the critical appraisal for each included study was provided. Specifically, tables were developed to present the answers to the questions within the critical appraisal tools, along with a narrative description of the strengths and limitations of the included studies within the main text of the report to provide the reader with an overview of the quality of the literature.

Meta-Analysis

The possibility of conducting meta-analyses was considered for OS, PFS, and AE outcomes (i.e., the outcomes identified as most important by the interviewed patient and clinical experts consulted) and all subgroups of interest. Specifically, clinical, methodological, and statistical characteristics of the included studies were explored, in consultation with clinical and statistical experts, to determine if the data were sufficiently homogeneous for pooling. Meta-analyses were deemed inappropriate and not conducted, and the reasons for these decisions were documented.

Reporting of Findings

The systematic review was prepared in consideration of relevant reporting guidelines (i.e., PRISMA statement,⁵³ Synthesis Without Meta-analysis [SWiM] guideline,⁵⁴ and Guidance for Reporting Involvement of Patients and the Public – Short Form [GRIPP2-SF] reporting checklist⁵⁵), and meets the criteria outlined in A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist.⁵⁶

Patient Engagement

CADTH involves patients, patient families, and patient groups to improve the quality and relevance of our assessments, ensuring that those affected by the assessments have an opportunity to contribute to them. CADTH has adopted the CADTH Framework for Patient

Engagement in Health Technology Assessment.⁵⁷ The framework includes Standards for Patient Involvement in Individual Health Technology Assessments and is used to support and guide our activities involving patients. CADTH engaged 1 adult cancer patient who has lived experience with SABR treatment for their oligometastatic cancer.

Invitation to Participate and Consent

A person with SABR experience was identified through CADTH's informal network of radiation oncologists. A CADTH patient engagement officer contacted potential participants by phone to explore their interest in becoming involved. The preliminary request described CADTH and the purpose and scope of this review, the purpose of the engagement, and the nature of the engagement activities. The patient engagement officer obtained this person's informed consent.

Engagement Activities

The objective of patient engagement is to inform the research team about the experience of SABR and to raise considerations and perspectives that are not available in clinical trials. The purpose is not to analyze the views and comments of the patient; rather, the patient's perspectives are used to help interpret the clinical evidence. A patient was and will be invited to reflect on their personal experiences at several time points during assessment, including:

- prior to clinical protocol finalization
- during drafting of the initial baseline clinical review
- upon completion of the baseline clinical review
- during the clinical review update(s) as part of the LSR phase
- upon transitioning the clinical review out of living mode.

The patient perspectives gained through engagement helped ensure the relevance of outcomes of interest for the clinical assessment and added comments on other key concepts that were initially identified through prior scoping activities. The involvement of patients prompted the research team to consider the possible need to explore avenues of analysis that may have otherwise been missed or underdeveloped. The involvement of patients enabled the research team to consider the evidence alongside an understanding of the wider experiences of patients and caregivers.

Once preliminary findings of the initial baseline review were available, the participant was invited to be interviewed. The conversation explored the patient's perceptions of key findings, including whether the findings were understandable, and whether they reflect personal experiences or understandings. Final conversations will be held with the participant upon completion of the final baseline clinical review. CADTH will share the key results of the full assessment and describe how engagement activities were used. A similar process for patient engagement will be followed during any updating of the clinical review during the LSR phase and when the clinical review transitions out of living mode.

Reporting

The reporting of this section follows the GRIPP2-SF reporting checklist.⁵⁵

Results

Quantity of Research Available

A total of 2,859 citations were identified in the literature search. Following screening of titles and abstracts, 2,726 citations were excluded and 133 were retrieved for full-text review. An additional 10 potentially relevant reports were retrieved from other sources (i.e., search alerts). Of these 143 potentially relevant articles, 131 publications were excluded for various reasons, and 9 unique studies (3 RCTs and 6 nonrandomized studies) in 12 publications met the inclusion criteria and were included in this review. One RCT (i.e., SABR-COMET) had 3 publications,^{32,58,59} and 1 nonrandomized study had 2 publications.^{60,61} No unique studies that met the inclusion criteria were submitted by stakeholders. Nine studies in 12 publications were relevant to research question 1,^{32,58-68} and 6 studies in 8 publications were relevant to research question 2.^{32,58,62,63,66-68} The study selection process (Figure 2) is outlined in Appendix 3 using a PRISMA flow chart. Lists of included and excluded citations, with details describing the rationale for those excluded, are presented in Appendix 4 and Appendix 5, respectively. CADTH acknowledges that there are randomized trials of metastasis-directed therapy for oligometastatic cancer that are not limited to SABR. However, given the focus of this HTA on SABR specifically, studies of metastasis-directed therapy that did not report results specific to SABR were excluded and can be found in Appendix 5.

Heterogeneity and Decisions Regarding Meta-Analysis

The included studies were generally considered to be too heterogeneous in terms of clinical, methodological, or statistical characteristics to be pooled in meta-analyses for OS, PFS, and AE outcomes and for the subgroups of interest. In 1 instance, a meta-analysis might have been appropriate for 2 studies but was deemed unlikely to add any statistical value to the narrative synthesis, as the point estimates from those studies matched closely in their direction, magnitude, and statistical significance. Thus, findings for all outcomes were synthesized narratively for this baseline review. The complete list of relevant studies for each comparison and the detailed rationale for not conducting meta-analyses is found in Appendix 6. In brief, sources of heterogeneity included differences across the studies in:

- different study designs (i.e., RCTs and nonrandomized studies needing to be analyzed separately, leading to a small numbers of studies)
- data unavailability (e.g., 2 relevant studies for the comparison of interest, but HRs reported for only 1 study)
- data variability (e.g., the AEs that were reported included different AE grades, treatment versus non-treatment-related AEs, or event data versus patient data)
- discordant results (i.e., large variability in the direction, magnitude, and statistical significance of the results).

Study Characteristics

Additional details regarding the characteristics of included studies are provided in Appendix 7.

Study Design, Year of Publication, Sample Size, and Funding

Question 1: Clinical Effectiveness

Three RCTs (in 5 publications^{32,58,59,62,63}) and 6 nonrandomized studies (1 prospective cohort study⁶⁴ and 5 retrospective cohort studies in 6 publications^{60,61,65-68}) were identified

regarding the clinical effectiveness of SABR (with or without SOC) versus SOC comparators. These studies were published between 2013 and 2020. Figure 3 identifies the number of publications by study year.

The sample size of the included studies ranged from 26 to 506 patients (RCTs: 29 to 99 patients; nonrandomized studies: 26 to 506 patients). Of the included studies, 3 received public funding,^{32,58,59,63,66} 1 disclosed that no financial support was provided to undertake the research,⁶⁷ and 5 studies did not report the source of funding.^{60,61,64,65,68,69} No studies reported being sponsored by industry.

Question 2: Safety

Three RCTs (in 4 publications^{32,58,63,69}) and 3 nonrandomized studies (all retrospective cohort studies⁶⁶⁻⁶⁸) were identified regarding the safety of SABR (with or without SOC) versus SOC comparators. These studies were published between 2016 and 2020 (Figure 3).

The sample size of the included studies ranged from 26 to 506 patients (RCTs: 29 to 99 patients; nonrandomized studies: 26 to 506 patients). Of the included studies, 3 received public funding,^{32,58,63,66} 1 disclosed that no financial support was provided to undertake the research,⁶⁷ and 2 did not report the source of funding.^{68,69}

Country of Origin

Question 1: Clinical Effectiveness

Two RCTs were conducted in the US^{63,69} and 1 RCT (in 3 publications)^{32,58,59} was conducted at multiple institutions across Canada, the Netherlands, UK, and Australia. The nonrandomized studies were conducted in Turkey,⁶⁵ the Netherlands,^{60,61,64} Italy,⁶⁸ and China.⁶⁷ One additional nonrandomized study⁶⁶ was conducted across multiple institutions across Belgium, Italy, France, Switzerland, UK, and Spain.

Question 2: Safety

Two RCTs were conducted in the US^{63,69} and 1 RCT (in 2 publications)^{32,58} was conducted across multiple institutions across Canada, the Netherlands, UK, and Australia. The nonrandomized studies were conducted in China⁶⁷ and Italy.⁶⁸ One additional nonrandomized study⁶⁶ was conducted across multiple institutions across Belgium, Italy, France, Switzerland, the UK, and Spain.

Patient Population

Question 1: Clinical Effectiveness

The median patient age ranged from 63⁶⁶ to 71⁶⁷ years, and males were more represented overall, given the prevalence of patients with primary prostate cancer in the included studies.

Consistent with our inclusion criteria, all studies included patients with oligometastatic cancer, as described by study authors as having limited metastatic lesions using terminology such as "oligo," "limited," or "few."^{32,58-68} The location of the primary tumour and metastatic sites varied widely across studies and, in some cases, within a study (i.e., in a single study, the included population may have included patients with different primary tumour locations or metastatic sites).

Type of primary tumour included breast,^{32,58,64} lung,^{32,58-61,64,69,70} kidney,^{60,61,64} colorectal,^{32,58-61,67,68} prostate,^{32,58,59,63-66,70} sarcoma,^{60,61} and other (non-specified).^{32,58-61,64} Most studies included patients who had some previous treatment of the primary tumour (3 RCTs,^{32,58,59,62,63} 6 nonrandomized studies^{60,61,64-68}).

All studies allowed for up to 5 metastatic lesions per patient with the exception of 2 studies,^{63,67} which included patients with up to 3 metastatic lesions. Locations of the metastases included bone,^{32,58,59,63-65,69} lymph nodes,^{32,58,59,65-67,69} soft tissue,^{63,64} brain,^{32,58,59} nasopharynx,⁶⁹ adrenal,^{32,58,59,69} lung,^{32,58-61,68,69} liver,^{32,58,59,64,69} and other.⁶⁴ Of note, in the RCT (SABR-COMET) that included patients with brain metastases (n = 1 metastatic lesion in the SABR intervention group; n = 3 metastatic lesions in the control group), all of those patients also had metastases in locations other than the brain.^{32,58,59}

Three nonrandomized studies^{60,61,67,68} included patients with metastasis to a single location in either the lung^{60,61,68} or liver.⁶⁷ Six studies (3 RCTs,^{32,58,63,69} 3 nonrandomized studies⁶⁴⁻⁶⁶) included patients with metastasis to multiple locations, 5 studies^{32,58,63-65,69} included patients with metastases in the bone and other sites, and 1 study⁶⁶ had patients with metastases in the lymph nodes of the pelvic and extra-pelvic areas.

Seven studies included at least some patients who had received previous treatment for metastases;^{32,58-61,64,66-69} the remaining 2 studies were unclear in their reporting of any history of treatment for oligometastases.^{63,65}

Question 2: Safety

The median patient age ranged from approximately 63⁶⁶ to 71⁶⁷ years, and males were more represented overall, given the prevalence of patients with primary prostate cancer in the included studies.

All studies included patients with oligometastatic cancer.^{32,58,63,66-69} The location of the primary tumour and metastatic sites varied widely across studies and, in some cases, within a study. Types of primary tumour included breast,^{32,58} lung,^{32,58,69} colorectal,^{32,58,67,68} prostate,^{32,58,63,66} and other (non-specified).^{32,58} Three RCTs^{32,58,63,69} and 3 nonrandomized studies⁶⁶⁻⁶⁸ included patients who all had any previous treatment of the primary tumour. Two studies included patients with metastasis to a single location (i.e., lung metastases^{67,68}); 3 studies included patients with metastasis in the bone and other sites, including lung, liver, brain, adrenal, mediastinum, axilla and nasopharynx,^{32,58,63,69} and 1 study had patients with metastasis in the lymph nodes of pelvic and extra-pelvic areas.⁶⁶ As noted previously, 4 patients in 1 RCT (SABR-COMET)^{32,58,59} with brain metastases (1 in the SABR group and 3 in the control group) also had metastases in locations other than the brain. Five studies included at least some patients who had previous treatment of metastases,^{32,58,66-69} and 2 studies were unclear in their reporting of any history of treatment for oligometastases.^{63,67}

Interventions and Comparators

Question 1: Clinical Effectiveness

The intervention of interest was SABR of any dose or fractionation alone or in combination with 1 or more concurrent or neoadjuvant therapies (i.e., SABR alone or in combination with SOC). In the included studies, 5 examined SABR alone,^{60,61,63,64,67,68} 2 examined SABR with systemic therapy,^{32,58,59,69} and 2 examined SABR with or without systemic therapy (i.e., hormone therapy, androgen deprivation therapy [ADT]) at the discretion of the physician.^{65,66} The dose used when administering SABR was study-dependent and varied based on the protocol used in consideration of the location(s) of the targeted metastatic site(s), and the frequency and number of fractions per lesion per patient (Appendix 7).

SABR was compared with SOC. The SOC comparators in the included studies comprised no therapy (i.e., observation),⁶³ surgery,^{60,61,68} systemic therapy (i.e., maintenance chemotherapy),⁶⁹

conventional radiotherapy (i.e., 3-dimensional conformal radiation therapy [3DCRT]),^{64,67} conventional radiotherapy (i.e., conventional fractionation radiotherapy or elective nodal radiotherapy [ENRT]) with or without systemic therapy (i.e., hormonotherapy, ADT) at the discretion of the physician,^{65,66} and palliative SOC.^{32,58,59} Specifically, palliative SOC offered to the SABR-COMET trial's control group included systemic therapy and palliative (not radical) radiotherapy to alleviate symptoms or prevent anticipated complications of progression.^{32,58,59}

For the 2 studies^{65,66} that had common treatments (i.e., systemic therapy) provided in both the intervention and control groups, the effects of those treatments were assumed to be the same in both groups, allowing the comparison of interest to distill down to SABR versus SOC for the sake of categorization in this review.

Question 2: Safety

Among 7 included studies, 4 examined SABR alone,^{63,67,68} 2 examined SABR with systemic therapy,^{32,58,69} and 1 examined SABR with or without systemic therapy (i.e., ADT) at the discretion of the physician.⁶⁶

The comparators included observation,⁶³ surgery,⁶⁸ systemic chemotherapy (i.e., maintenance chemotherapy),⁶⁹ conventional radiotherapy (i.e., 3DCRT),⁶⁷ a combination of radiotherapy with palliative intent and systemic therapy,^{32,58} and radiotherapy (i.e., ENRT) with or without systemic therapy (i.e., ADT) at the discretion of the physician.⁶⁶

Outcomes

Question 1: Clinical Effectiveness

All studies captured at least 1 key outcome (i.e., OS, PFS) to answer this research question. Seven studies examined OS (2 RCTs,^{32,58,69} 5 nonrandomized studies^{60,61,64,65,67,68}), and 7 studies examined PFS (3 RCTs,^{32,58,63,69} 4 nonrandomized studies^{60,61,64,65,68}).

Additional outcomes of interest included health-related QoL (3 studies: 2 RCTs^{32,58,59,63} and 1 nonrandomized study⁶⁴) and LC (2 studies: 1 RCT,^{32,58} 1 nonrandomized study^{60,61}). The 2 RCTs assessed health-related QoL using validated tools such as the Brief Pain Inventory (Short Form)⁶³ and the Functional Assessment of Cancer Therapy–General (FACT-G).^{32,58,59} The nonrandomized study⁶⁴ measured QoL using validated questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 15 Palliative (QLQ-C15-PAL), Brief Pain Inventory, and the EuroQol 5-Dimensions questionnaire (EQ-5D). None of the included studies explored freedom from progression or systemic therapy use after treatment with SABR.

In the included studies, the length of follow-up was variable and also reported inconsistently (i.e., some studies reported total follow-up,^{58,60,61,63,65-67,69} and others reported follow-up separately for the intervention and comparator^{32,64,68}). The shortest follow-up point for a key outcome was a median follow-up of 9.6 months (interquartile range [IQR], 2.4 to 30.2 months);⁶⁹ the longest follow-up point was a median follow-up of 91 months (IQR, 69.6 to 117.6 months).⁶¹

Question 2: Safety

Six studies examined AEs (3 RCTs,^{32,58,63,69} 3 nonrandomized studies⁶⁶⁻⁶⁸). The studies used version 3 or version 4 of the Common Terminology Criteria for Adverse Events (CTCAE) or the Radiation Therapy Oncology Group (RTOG) assessment tool to evaluate AEs for SABR compared with its comparators. Reporting on AEs varied among studies: 3 reported AE

grades of 1 or higher,^{63,67,69} 1 reported AE grades of 2 or higher,^{32,58} 1 reported AE grades of 0 or higher,⁶⁸ and 1 reported AE grades of 3 or higher.⁶⁶

Critical Appraisal of Individual Studies

A summary of the critical appraisal for RCTs can be found in Table 3 and in Table 4 for nonrandomized studies. Appendix 8 presents details of the critical appraisal of both the included RCTs (Table 18) and nonrandomized studies (Table 19). Overall, each of the included studies exhibited some risk of bias, described subsequently.

Risk of Bias in RCTs

The risk of bias in 3 RCTs (from 5 publications^{32,58,59,63,69}) was assessed with RoB 2 (Table 3).

For 2 of the included RCTs,^{32,58,59,63} there was a high risk of bias arising from the randomization process. Though both studies used a computerized random allocation sequence, no information was provided about whether the allocation sequence was concealed until participants were enrolled and assigned to the intervention.^{32,58,59,63} Moreover, some baseline differences between intervention groups may suggest a problem with the randomization process, although no statistical comparisons were conducted for them: in Phillips et al.,⁶³ the control arm had a higher Gleason score (from the grading classification system that helps in evaluating the prognosis of patients with prostate cancer) and a higher proportion of patients in the intervention arm received prior ADT; in SABR-COMET,^{32,58,59} the intervention arm had a higher proportion of patients with prostate cancer. Generally, the methods described in the third RCT by Iyengar et al.⁶⁹ were brief in nature, making the risk of bias for various categories uncertain; therefore, it is possible the risk of bias is higher or lower than what was reported (i.e., the quality of the reporting might have impacted the critical appraisal). Due to the lack of information provided by Iyengar and colleagues,⁶⁹ there were some concerns of bias arising from the randomization process. Iyengar et al.⁶⁹ did not provide details about whether the allocation sequence was random and, if so, concealed until participants were enrolled and assigned to the intervention groups. However, the authors reported no significant differences in baseline characteristics between the 2 arms, which might argue against there being any serious problem with the randomization process.⁶⁹

There were some concerns of bias due to deviations from intended interventions for all 3 RCTs.^{32,58,59,63,69} All 3 RCTs were open-label studies, meaning both the participants and the individuals delivering the interventions were aware of the intervention assignments during the trial, which could have led to some deviations. However, although 1 patient from the control group in the SABR-COMET study^{32,58,59} withdrew consent for further follow-up to pursue SABR, this single deviation was unlikely to have affected the balance between the groups or the results due to the relatively large sample size. Similarly, Iyengar et al.⁶⁹ reported that 2 patients crossed over from the control arm to the intervention arm, but these deviations were unlikely to have affected the interpretation of the results. For the other RCT,⁶³ no information was provided about whether there were deviations from the intended intervention that arose because of the trial context.

The included RCTs^{32,58,59,63,69} used appropriate analyses to estimate the effect of intervention assignments using an intention-to-treat (ITT) analysis. For all outcomes of interest for all included RCTs,^{32,58,59,63,69} outcome data were available for all or nearly all participants randomized. Thus, there was a low risk of bias due to missing outcome data for all included RCTs.

The level of risk of bias in the measurement of the outcome depended on the RCT being assessed and the type of outcome explored, ranging from low risk to some concerns. Generally, the method of measurement and analysis for all included outcomes for all RCTs was likely appropriate (e.g., the Kaplan-Meier method was used to estimate survival outcomes, CTCAE was used to classify AEs, FACT-G was used to assess QoL).^{32,58,59,63,69} However, none of the studies reported having adjusted for multiplicity in their outcome measures, suggesting that the type I error rate might have been inflated if multiple testing was conducted. For 1 RCT, outcome assessors were aware of the intervention received by study participants;⁶³ however, this was unclear for the other 2 RCTs.^{32,58,59,69} However, it is unlikely that the measurement or ascertainment of the outcomes would have been different between the intervention groups.^{32,58,59,63,69} For outcomes that inherently have some subjectivity in the assessment (e.g., outcomes that involve assessment of a radiograph or clinical examination based on medical records, such as LC, AEs, and QoL outcomes), it is possible that the assessment of these outcomes could have been influenced by the knowledge of the intervention received.

There was a low risk of bias in the selective reporting of outcomes for the included RCTs,^{32,58,59,63,69} as data analyses and reported results were all in accordance with a pre-specified analysis plan indicated in the corresponding protocols.^{32,58,59,63,69}

One RCT^{32,58,59} reported a similar median follow-up between the treatment arms, but the range was wider in the comparator arm. The other 2 RCTs^{63,69} reported only the median follow-up of the total population with a wide IQR, without providing follow-up details for each treatment arm. Therefore, it was unclear whether there was any difference in the follow-up duration between the treatment arms in those studies.

Overall risk-of-bias judgment revealed that 2 RCTs^{32,58,59,63} were considered to have an overall high risk of bias and 1 RCT⁶⁹ as having some concerns of bias overall.

Table 3: Risk of Bias Summary – RCTs (Cochrane Risk of Bias Tool 250)

First author (publication year) Relevant for clinical research question(s)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk-of-bias judgment
Phillips et al. (2020) ⁶³ 1, 2	High risk	Some concerns	PFS: Low risk AEs: Low risk QoL: Low risk	PFS: Low risk AEs: Some concerns QoL: Some concerns	Low risk	High risk
SABR-COMET Palma et al. (2019) ³² , Palma et al. (2020) ⁵⁸ , Olson et al. (2019) ⁵⁹ 1, ^{32,58,59} 2 ^{32,58}	High risk	Some concerns	OS: Low risk PFS: Low risk AEs: Low risk LC: Low risk QoL: Low risk	OS: Low risk PFS: Low risk AEs: Some concerns LC: Low risk QoL: Some concerns	Low risk	High risk
Iyengar et al. (2018) ⁶⁹ 1, 2	Some concerns	Some concerns	OS: Low risk PFS: Low risk AEs: Low risk	OS: Low risk PFS: Low risk AEs: Some concerns	Low risk	Some concerns

AE = adverse event; LC = lesional control; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; QoL = quality of life.

Risk of Bias in Nonrandomized Studies

The risk of bias in 6 nonrandomized studies (from 7 publications)^{60,61,64-68} was assessed using RoBANS^{51,52} (Table 4).

The risk of selection bias from the domain related to the possibility of the target group comparisons varied between the included studies: 1 study was considered to be at low risk of bias because pertinent baseline characteristics were balanced between groups,⁶⁷ and 4 studies were considered to be at high risk of bias because the intervention groups differed in some of the main baseline characteristics.^{60,61,64,66,68} For instance, 1 study^{60,61} had older patients (i.e., higher in median age) receiving SABR, 2 studies (in 3 publications)^{60,61,64} had higher proportions of patients in the SABR group who had received prior treatment for metastatic disease and had imbalances in the primary tumour location between groups, 1 study⁶⁶ had a higher proportion of patients receiving adjuvant ADT in the comparator group compared with SABR, and 1 study⁶⁸ had a higher proportion of patients in the SABR group who had been diagnosed with metastases at a later period compared with surgery. Given various differences in baseline characteristics, it is difficult to predict the direction of bias. The remaining study⁶⁵ was considered to have an unclear risk of bias because the baseline characteristics were not reported for each group, preventing comparison.⁶⁵

All nonrandomized studies were at low or unclear risk of selection bias for the target group selection domain. Studies were considered to be at low risk of bias when the participant

recruitment strategy (e.g., standard of inclusion or exclusion, selection method) was the same for both groups.^{64,67,68} Studies were considered to have an unclear risk of bias when the participant recruitment strategy was not clearly described (e.g., unknown whether participants selected from different institutions were balanced between groups).^{60,61,65,66}

All nonrandomized studies were at a low risk or unclear risk of selection bias due to confounders: low-risk studies confirmed confounders and considered them during the planning and analysis stages,^{60,61,64,66,68} and the studies with unclear risk of bias were not clear for at least 1 outcome if confounders were confirmed or considered during the planning and analysis stages.^{65,67}

For all included nonrandomized studies,^{60,61,64-68} there was a low risk of performance bias (i.e., exposure measurement domain), since the data were obtained from medical records — and for reasons of detection bias (i.e., blinding of assessor's domain) — as the main end points were time-to-event (survival) outcomes (i.e., objective outcomes).

For all outcomes of all included nonrandomized studies,^{60,61,64-68} the outcome assessment was probably appropriate (i.e., low risk of confirmation bias), since outcome data were confirmed with medical records. One study⁶⁴ reported having adjusted for multiplicity but only for QoL outcome measures, and no other study reported having adjusted for multiplicity in its outcome measures, suggesting the type I error rate might have been inflated if multiple testing was conducted.

When considering attrition bias via the incomplete outcome data domain, 2 studies were at low risk of bias, given there were no missing data in the analysis of all reported outcomes,^{60,61,68} and 3 studies had an unclear risk of bias, as it was unclear whether all participant data were included in the analyses.⁶⁵⁻⁶⁷ One study⁶⁴ had a low risk of attrition bias for OS and PFS outcomes (i.e., all data included in analyses), but a high risk of bias for pain response and QoL outcomes because not all patient data were included in the analyses for these outcomes (i.e., study authors excluded all patients with no pain at baseline).

One study had been publicly registered a priori (ClinicalTrials.gov NCT02356497; low risk of reporting bias).⁶⁴ The remaining studies did not mention having or registering a protocol a priori; therefore, it is unclear whether there was any selective outcome reporting (i.e., reporting bias) for these studies.^{60,61,65-68}

Regarding follow-up duration, 2 studies^{64,68} reported that the median follow-up in the intervention group was much shorter compared with that in the comparator group. Four studies^{60,61,65-67} reported the median follow-up of the total population. It was therefore unclear whether there was any difference in the duration of follow-up between the treatment arms in those studies.

Overall risk-of-bias judgment revealed that 4 studies^{60,61,64,66,68} were considered to have an overall high risk of bias and that 2 studies^{65,67} had some concerns of bias overall.

Table 4: Risk of Bias Summary – Nonrandomized Studies (RoBANS51,52)

First author (publication year) Relevant for clinical research question(s)	The possibility of the target group comparisons	Target group selection	Confounder	Exposure measurement	Blinding of assessors	Outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias judgment
	Risk of selection bias due to selection of inappropriate comparison target group	Risk of selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group	Risk of selection bias due to inappropriate confounder confirmation and consideration	Risk of performance bias due to inappropriate intervention or inappropriate exposure measurement	Risk of confirmation bias due to inappropriate blinding of assessors	Risk of confirmation bias due to inappropriate outcome assessment methods	Risk of attrition bias due to inappropriate handling of incomplete data	Risk of reporting bias due to selective outcome reporting	
Hurmuz et al. 2020 ⁶⁵ 1	Unclear	Unclear	Unclear	Low	Low	OS: Low PFS: Low	OS: Unclear PFS: Unclear	Unclear	Some concerns
van de Ven et al. (2020) ⁶⁴ 1	High	Low	Low	Low	Low	OS: Low PFS: Low Pain response: Low QoL: Low	OS: Low PFS: Low Pain response: High QoL: High	Low	High risk
De Bleser et al. (2019) ⁶⁶ 1, 2	High	Unclear	Low	Low	Low	AEs: Low	AEs: Unclear	Unclear	High risk
He et al. (2018) ⁶⁷ 1, 2	Low	Low	Unclear	Low	Low	OS: Low AEs: Low	OS: Unclear AEs: Unclear	Unclear	Some concerns
Filippi et al. (2016) ⁶⁸ 1, 2	High	Low	Low	Low	Low	OS: Low PFS: Low AEs: Low	OS: Low PFS: Low AEs: Low	Unclear	High risk
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ⁶¹ 1, 2	High	Unclear	Low	Low	Low	OS: Low PFS: Low LC: Low	OS: Low PFS: Low LC: Low	Unclear	High risk

AE = adverse event; LC = lesional control; OS = overall survival; PFS = progression-free survival; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; QoL = quality of life.

Data Analysis and Synthesis

Table 5 presents a high-level summary of the findings of the included studies on the clinical effectiveness and safety of SABR for the treatment of patients with oligometastatic cancer, which were grouped into 2 main comparisons (i.e., SABR + SOC versus SOC alone, and SABR versus SOC). Appendix 9 presents the main study findings with regard to OS (Table 20), PFS (Table 21), health-related QoL (Table 22, Table 23), and AEs (Table 24).

Due to the limited amount of available data, subgroup analyses were not possible.

Table 5: High-Level Summary of the Findings

Overarching comparison	Intervention vs. comparator	Effects by OUTCOME						
		OS	PFS	FFP	HRQoL	LC	Systemic therapy use	AEs
SABR + SOC vs. SOC	SABR + systemic therapy vs. systemic therapy ^{32,58,59}	Short-term F/U: NS Longer-term F/U: +	Short-term F/U: + Longer-term F/U: +	NR	NS	Short-term F/U: + Longer-term F/U: +	NR	Related AE grade ≥ 2 -; other NS
	SABR + chemotherapy vs. chemotherapy ⁶⁹	?	+	NR	NR	NR	NR	?
SABR vs. SOC	SABR vs. observation ⁶³	NR	+	NR	NS	NR	NR	?
	SABR ± hormonotherapy vs. conventional fractionation radiotherapy ± hormonotherapy ⁶⁵	NS	+	NR	NR	NR	NR	NR
	SABR vs. 3DCRT ⁶⁴	+	+	NR	NS	NR	NR	NR
	SABR ± ADT vs. ENRT ± ADT ⁶⁶	NR	NR	NR	NR	NR	NR	+
	SABR vs. 3DCRT ⁶⁷	NS	NR	NR	NR	NR	NR	NS
	SABR vs. various resections ⁶⁸	NS	-	NR	NR	NR	NR	?
	SABR vs. PME ^{60,61}	NS	NS	NR	NR	NS	NR	NR

+ = intervention more favourable than comparator; - = intervention less favourable than comparator; ? = not compared statistically; 3DCRT = 3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; AE = adverse event; ENRT = elective nodal radiotherapy; FFP = free from progression; F/U = follow-up; LC = lesional control; NR = not measured or not reported; NS = not statistically significant; OS = overall survival; PFS = progression-free survival; PME = pulmonary metastasectomy; SABR = stereotactic ablative radiotherapy; SOC = standard of care; vs. = versus.

Question 1: Clinical Effectiveness

SABR With SOC Versus SOC Alone

Overall Survival

From 2 RCTs using ITT analyses,^{32,58,69} with an overall risk of bias of either high or with some concerns and considering multiple metastatic sites and up to 5 oligometastases in patients previously treated for their primary tumour, there is some evidence suggesting an OS benefit associated with SABR plus SOC compared with SOC alone (Table 6). The initial findings from the SABR-COMET RCT (N = 99 patients)³² found longer median OS and a lower HR for OS in the SABR plus systemic therapy (n = 66 patients) compared with systemic therapy (n = 33; i.e., systemic therapy with patients being allowed to receive radiotherapy with palliative intent) in patients with multiple primary tumour locations. The median OS was 41 months (95% confidence interval [CI], 26 to not reached) for SABR plus systemic therapy and 28 months (95%CI, 19 to 33) for systemic therapy alone. The unadjusted HR was 0.57 (95% CI, 0.30 to 1.10; P = 0.09) with a median follow-up of 26 months (IQR, 23 to 37) for SABR plus systemic therapy and 25 (IQR, 19 to 54) months for systemic therapy. A longer surveillance period (median follow-up for both arms was 51 months; IQR, 46 to 58 months) revealed a significant difference in OS in favour of SABR plus systemic therapy compared with systemic therapy alone (unadjusted HR was 0.47; 95% CI, 0.27 to 0.81; P = 0.006).⁵⁸ the Iyengar et al. RCT⁶⁹ of 29 patients with primary lung cancer provided limited OS findings for their study: for the SABR plus maintenance chemotherapy intervention arm (n = 14), median OS was not reached during the investigation period (i.e., more than half the patients were still alive); for the maintenance chemotherapy arm, median OS was nearly 1 year for patients who did not cross over (n = 13) and was 17 months for patients who crossed over to receive SABR at oligoprogression (n = 2). No HRs for OS were reported and the authors reported their study was not powered to show a statistical difference in survival.⁶⁹ Both RCTs^{32,58,69} had patients who had been previously treated for their metastases.

Table 6: OS Comparing SABR With SOC Versus SOC

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Death events; n	2-year OS rate, % (95% CI)	5-year OS rate, % (95% CI)	Median OS (95% CI); months	Unadjusted HR (95% CI)
RCTs							
SABR-COMET Palma et al. (2019) ³² and Palma et al. (2020) ⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy (n = 33) Short-term F/U Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • Systemic therapy: 25 (19 to 54) months ³² Long-term F/U Median F/U (IQR): • Total: 51 (46 to 58) months ⁵⁸	Age, median (IQR): • SABR + SOC: 66.8 (42.8 to 89.4) years • SOC: 68.6 (44.2 to 87.0) years % male: • SABR + SOC: 61 • SOC: 58 Primary tumour location: Breast, colorectal, lung, prostate, and other (not described in publication) Met site: Multiple Number of mets: ≤ 5 Mets location: Adrenal, bone, liver, lung, other: • brain (3 lesions in control; 1 lesion in SABR+SOC) • lymph nodes (1 lesion in control; 3 lesions in SABR+SOC) • para-renal (1 in SOC) Previous tx primary tumour: Yes Previous tx mets: Yes	Short-term F/U: 24 vs. 16 Long-term F/U: 35 vs. 24	Short- and long-term F/U: NR	Short-term F/U: NR Long-term FU: 42.3 (28 to 56) vs. 17.7 (6 to 34)	Short-term F/U: 41 (26 to not reached) vs. 28 (19 to 33) Long-term F/U: 50 (29 to 83) vs. 28 (18 to 39)	Short-term F/U: 0.57 (0.30 to 1.10); P = 0.09 Long-term F/U: 0.47 (0.27 to 0.81); P = 0.006

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Death events; n	2-year OS rate, % (95% CI)	5-year OS rate, % (95% CI)	Median OS (95% CI); months	Unadjusted HR (95% CI)
Iyengar et al. (2018) ⁶⁹	SABR + chemotherapy (n = 14) vs. chemotherapy (n = 15) Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	Age, median (IQR): • SABR + maintenance chemotherapy: 63.5 (51.0 to 78.0) years • maintenance chemotherapy: 70.0 (51.0 to 79.0) years % male: • SABR + maintenance chemotherapy: 64.3 • maintenance chemotherapy: 73.3 Primary tumour location: lung Met site: multiple Number of mets: ≤ 5 Mets location: Lung, adrenal, mediastinum, axilla, liver, nasopharynx, bone (rib, spine) Previous tx primary tumour: Yes Previous tx mets: Yes	NR	NR	NR	Not reached (NR) vs. about 1 year without crossover; 17 months with crossover (NR)	NR

CI = confidence interval; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; met = metastasis; mets = metastases; NR = not reported; OS = overall survival; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

Progression-Free Survival

In 2 RCTs,^{32,58,69} either at high risk of bias or with some concerns of bias overall, there is some early evidence to suggest that SABR plus systemic therapy may be more effective than systemic therapy alone for PFS^{32,58,69} (Table 7). Both RCTs^{32,58,69} included patients with multiple metastatic sites and a maximum of 5 oligometastases.

One RCT (SABR-COMET) with 2 publications^{32,58} reported a significant advantage in PFS for patients with multiple primary tumour locations who received SABR plus systemic therapy compared with systemic therapy alone. The initial findings from the SABR-COMET RCT³² found a significant PFS benefit for SABR plus systemic therapy compared with systemic therapy alone (unadjusted HR was 0.47; 95% CI, 0.30 to 0.76; P = 0.0012; median follow-up was 26 months [IQR, 23 to 37 months] for SABR plus systemic therapy, and 25 months [IQR, 19 to 54] for systemic therapy alone). A longer surveillance period (median follow-up for both arms was 51 months; IQR, 46 to 58 months) revealed similar PFS benefits in favour of SABR plus systemic therapy (unadjusted HR was 0.48; 95% CI, 0.31 to 0.76; P = 0.001).⁵⁸ Another RCT by Iyengar et al.⁶⁹ of patients with primary lung cancer also reported a significant PFS benefit for SABR plus maintenance chemotherapy compared with maintenance chemotherapy alone (unadjusted HR was 0.304; 95% CI, 0.113 to 0.815; P = 0.01). Both RCTs^{32,58,69} had patients whose primary tumour and metastases had been previously treated.

Table 7: PFS Comparing SABR With SOC Versus SOC

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Progression events; n	4-year PFS rate, % (95% CI)	5-year PFS rate, % (95% CI)	Median PFS (95% CI); month	Unadjusted HR (95% CI)
RCTs							
SABR-COMET Palma et al. (2019) ³² Palma et al. (2020) ⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy alone (n = 33) Short-term F/U Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • systemic therapy: 25 (19 to 54) months ³² Long-term F/U Median F/U (IQR): Total: 51 (46 to 58) months ⁵⁸	Age, median (IQR): • SABR + SOC: 66.8 (42.8 to 89.4) years • SOC: 68.6 (44.2 to 87.0) years % male: • SABR + SOC: 61 • SOC: 58 Primary tumour location: Breast, colorectal, lung, prostate, and other Met site: Multiple Number of mets: ≤ 5 Mets location: adrenal, bone, liver, lung, other: • brain (3 lesions in control; 1 lesion in SABR + SOC) • lymph nodes (1 lesion in control; 3 lesions in SABR+SOC) • para-renal (1 in SOC) Previous tx primary tumour: Yes Previous tx mets: Yes	Short-term F/U: 39 vs. 28 Long-term F/U: 45 vs. 29	Short-term F/U: NR Long-term F/U: 21.6 (12 to 33) vs. 3.2 (0 to 14)	Short-term F/U: NR Long-term F/U: 17.3 (8 to 30) vs. 0 (NA)	12 (6.9 to 30.4) vs. 6.0 (3.4 to 7.1) Long-term F/U: 11.6 (6.1 to 23.4) vs. 5.4 (3.2 to 6.8)	0.47 (0.30 to 0.76); P = 0.0012 Long-term F/U: 0.48 (0.31 to 0.76); P = 0.001

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Progression events; n	4-year PFS rate, % (95% CI)	5-year PFS rate, % (95% CI)	Median PFS (95% CI); month	Unadjusted HR (95% CI)
Iyengar et al. (2018) ⁶⁹	SABR + chemotherapy (n = 14) vs. chemotherapy alone (n = 15) Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	Age, median (IQR): <ul style="list-style-type: none"> SABR + maintenance chemotherapy: 63.5 (51.0 to 78.0) years maintenance chemotherapy: 70.0 (51.0 to 79.0) years % male: <ul style="list-style-type: none"> SABR + maintenance chemotherapy: 64.3 maintenance chemotherapy: 73.3 Primary tumour location: Lung Met site: Multiple Number of mets: ≤ 5 Mets location: Lung, adrenal, mediastinum, axilla, liver, nasopharynx, bone (rib, spine) Previous tx primary tumour: Yes Previous tx mets: Yes	4 vs. 10	NR	NR	9.7 (NR) vs. 3.5 (NR)	0.304 (0.113 to 0.815); P = 0.01

CI = confidence interval; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; met = metastasis; mets = metastases; NR = not reported; PFS = progression-free survival; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

Freedom From Progression

None of the included studies explored freedom from progression. Consequently, no summary of evidence has been conducted.

Health-Related QoL

One RCT with 3 publications^{32,58,59} with an overall high risk of bias reported no significant differences between SABR plus systemic therapy and systemic therapy in health-related QoL outcomes (Table 8). The SABR-COMET study reported no significant differences between the 2 groups at 6 months in the patient-reported FACT-G outcome measure used to assess health-related QoL (FACT-G total, mean [standard deviation] for SABR plus systemic therapy: 82.6 [16.6] versus systemic therapy: 82.5 [16.4]; P = 0.99).³² There were also no significant differences between the 2 groups when examining subscales of the FACT-G tool at 6 months (i.e., physical, social, emotional, functional: P > 0.40 for all).³² The SABR-COMET trial also examined the same QoL outcome measures over 42 months and over 5 years.⁵⁹ At both time points, no significant differences were found between the 2 groups (P values ranged from 0.17 to 0.98).^{58,59} Thus, the SABR-COMET study concluded SABR plus systemic therapy

was not associated with a QoL detriment.^{32,58,59} This RCT^{32,58,59} included patients with multiple primary tumour locations and multiple metastatic sites with up to 5 oligometastases. Patients had been previously treated for their primary tumour and metastases.

Table 8: Health-Related QoL Comparing SABR With SOC Versus SOC Alone

Study	Study characteristics	Tool, follow-up, results
SABR-COMET Palma et al. (2019), ³² Palma et al. (2020), ⁵⁸ Olson et al. (2019) ⁵⁹	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • SABR plus + systemic therapy: 66.8 (42.8 to 89.4) years • systemic therapy: 68.6 (44.2 to 87.0) years <p>% male:</p> <ul style="list-style-type: none"> • SABR plus systemic therapy: 61 • systemic therapy: 58 <p>Primary tumour location: Breast, colorectal, lung, prostate, and other</p> <p>Mets sites: Multiple</p> <p>Number of mets: ≤ 5</p> <p>Mets location: adrenal, bone, liver, lung, other:</p> <ul style="list-style-type: none"> • brain (3 lesions in control; 1 lesion in SABR plus systemic therapy) • lymph nodes (1 lesion in control; 3 lesions in SABR plus systemic therapy) • para-renal (1 in systemic therapy) <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Yes</p>	<p>QoL (tool: FACT-G; 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being)</p> <p>QoL results:</p> <p>SABR plus systemic therapy versus systemic therapy alone³²</p> <ul style="list-style-type: none"> • FACT-G at 6 months, mean (SD): Total score:^a 82.6 (16.6) versus 82.5 (16.4); P = 0.99 <p>Subscales:</p> <p>Physical: 22.4 (4.8) versus 23.1 (4.9); P = 0.54</p> <p>Functional: 19.4 (5.8) versus 18.8 (7.0); P = 0.74</p> <p>Emotional: 18.1 (5.1) versus 18.3 (4.3); P = 0.87</p> <p>Social: 22.8 (5.1) versus 21.8 (6.3); P = 0.48</p> <p>SABR plus systemic therapy versus systemic therapy alone⁵⁹</p> <ul style="list-style-type: none"> • FACT-G over 42 months: Total score (P = 0.42) <p>Subscales:</p> <p>Physical (P = 0.98)</p> <p>Functional (P = 0.59)</p> <p>Emotional (P = 0.82)</p> <p>Social (P = 0.17)</p> <p>SABR plus systemic therapy versus systemic therapy alone⁵⁸</p> <ul style="list-style-type: none"> • FACT-G over 5 years: Total score (P = 0.98) <p>Subscales:</p> <p>Physical (P = 0.72)</p> <p>Functional (P = 0.47)</p> <p>Emotional (P = 0.77)</p> <p>Social (P = 0.19)</p>

FACT-G = Functional Assessment of Cancer Therapy–General; met = metastasis; mets = metastases; IQR = interquartile range; QoL = quality of life; SABR = stereotactic ablative radiotherapy; SD = standard deviation; SOC = standard of care; tx = treatment.

^aTotal score = sum of FACT-G physical, social, emotional, and functional well-being scores.

Lesional Control

Limited data from 1 RCT^{32,58} with an overall high risk of bias provided inconclusive evidence about LC to assess whether SABR plus SOC is more effective than SOC alone (Table 9).

The SABR-COMET RCT^{32,58} found improved crude LC rates for SABR plus systemic therapy

compared with systemic therapy alone during initial follow-up (75% versus 49%; P = 0.0010; median follow-up: 26 [IQR, 23 to 37] months for SABR plus systemic therapy; 25 [IQR, 19 to 54] months for systemic therapy)³² and after longer surveillance (63% versus 46%; P = 0.039; median follow-up for both arms 51 [IQR, 46 to 58] months).⁵⁸ HRs were not calculated for this outcome.^{32,58} This RCT^{32,58} included patients with multiple primary tumour locations and multiple metastatic sites with up to 5 oligometastases. Patients had been previously treated for their primary tumour and metastases.

Table 9: Lesional Control Comparing SABR With SOC Versus SOC

Study	Treatments (intervention vs. comparator)	Study characteristics	Crude LC rate, % (95% CI)
RCTs			
SABR-COMET Palma et al. (2019) ³² Palma et al. (2020) ⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy (n = 33) Short-term F/U Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • systemic therapy: 25 (19 to 54) months ³² Long-term F/U Median F/U (IQR): Total: 51 (46 to 58) months ⁵⁸	Age, median (IQR): • SABR + systemic therapy: 66.8 (42.8 to 89.4) years • systemic therapy: 68.6 (44.2 to 87.0) years % male: • SABR + systemic therapy: 61 • systemic therapy: 58 Primary tumour location: Breast, colorectal, lung, prostate, and other Met site: Multiple Number of mets: ≤ 5 Mets location: Adrenal, bone, liver, lung, other: • brain (3 lesions in control; 1 lesion in SABR + systemic therapy) • lymph nodes (1 lesion in control; 3 lesions in SABR + systemic therapy) • para-renal (1 in systemic therapy) Previous tx primary tumour: Yes Previous tx mets: Yes	Short-term F/U: 75 (NR) vs. 49 (NR), P = 0.0010 Long-term F/U: 63 (NR) vs. 46 (NR), P = 0.039

CI = confidence interval; F/U = follow-up; IQR = interquartile range; LC = lesional control; met = metastasis; mets = metastases; NR = not reported; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; tx = treatment; vs. = versus.

Systemic Therapy Use

None of the included studies explored systemic therapy use after treatment with SABR. Consequently, no summary of evidence has been conducted.

SABR Versus SOC

Overall Survival

Five nonrandomized studies^{60,61,64,65,67,68} at either high risk of bias or with some concerns of bias overall provided inconclusive evidence about OS to determine whether SABR is more effective than SOC (Table 10); 4 studies did not report any significant differences between SABR and SOC for OS measures reported (i.e., OS rates, unadjusted HRs, adjusted

HRs),^{60,61,65,67,68} and 1 study found an OS benefit for SABR when compared with 3DCRT.⁶⁴ None of the studies reported whether they performed a sample size calculation to obtain enough power to determine a statistical difference between groups for OS.

Hurmuz et al.⁶⁵ found no OS benefit for SABR with or without hormonotherapy (n = 129) at 2 years compared with conventional fractionation radiotherapy with or without hormonotherapy (n = 47) in patients with controlled primary prostate cancer with multiple metastatic sites and a maximum of 5 oligometastases. As patients from both arms optionally received hormonotherapy, the comparison in this study was considered to be SABR versus conventional fractionation radiotherapy. The 2-year OS rate was 87.7% (95% CI not reported) for the SABR group compared with 87.3% (95% CI not reported) for the conventional fractionation radiotherapy group (P = 0.91; median follow-up for both arms was 22.9 [IQR, 3.3 to 77.8] months). No HRs were provided by this study.⁶⁵

Filippi et al.⁶⁸ compared SABR (n = 28) with surgery (n = 142) for lung oligometastases (up to 5 lesions) from previously controlled colorectal cancer and found no significant differences in OS between groups according to the unadjusted HR of 1.7 (95% CI, 0.84 to 3.43), and adjusted HR of 1.71 (95% CI, 0.82 to 3.54). This study was highly imbalanced in terms of numbers of patients in each cohort (i.e., n = 28 in the SABR group versus n = 142 in the surgery group), which was exacerbated by a higher proportion of patients who died (i.e., 36% versus 26%) and more patients lost to follow-up at 30 months (i.e., 7 versus 1) in the SABR group compared with the surgery group. That imbalance might have led to the large difference in median follow-up between the 2 groups (i.e., SABR: 27 [IQR, 16.1 to 71.7] months versus surgery: 45.8 [IQR, 13.6 to 107.1] months) and potentially to the large uncertainty in the HR estimates.

Furthermore, another nonrandomized study compared OS outcomes at both short- and long-term follow-up time points with SABR (n = 42) versus surgery (n = 68) in patients with multiple primary tumour locations that metastasized to the lung with up to 5 oligometastases.^{60,61} All patients had been previously treated for their primary tumour. The median short-term follow-up was 43 (IQR, 36 to 60) months⁶⁰ and the median long-term follow-up was 91.2 (IQR, 69.6 to 117.6) months.⁶¹ Regardless of length of follow-up, no significant differences were found in OS between groups: the unadjusted HR for short-term follow-up was 0.79 (95% CI, 0.43 to 1.42); the adjusted HR for short-term follow-up was not reported. The unadjusted HR for long-term follow-up was 1.11 (0.70 to 1.75), and the adjusted HR for long-term follow-up was 0.76 (95% CI, 0.38 to 1.54).^{60,61}

He et al.⁶⁷ compared SABR (n = 11) with 3DCRT (n = 15) in patients with primary colorectal cancer that metastasized to the liver with up to 3 oligometastases. All patients had been previously treated for their primary tumour. With a median follow-up of 13 months across groups, the study⁶⁷ did not find an OS benefit for SABR when compared with 3DCRT (unadjusted HR: 0.61; 95% CI, 0.23 to 1.65). No other results with statistical testing were reported.⁶⁷

Van de ven and colleagues⁶⁴ found an OS benefit for the SABR group (n = 65) compared with the 3DCRT group (n = 66; unadjusted HR: 0.44; 95% CI, 0.21 to 0.81) in patients with multiple primary tumour locations that metastasized to the bone and other locations with up to 5 oligometastases, despite a significantly shorter time of follow-up in the SABR group (i.e., patients in the SABR group had a median follow-up of 25 [IQR, 5 to 52] months, and patients in the 3DCRT group had a median follow-up 46 [IQR, 9 to 55] months).

Table 10: OS Comparing SABR Versus SOC

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadjusted HR (95% CI)	Adj HR (95% CI)
				1-year	2-year	3-year	4-year	5-year			
NRSS											
Hurmuz et al. (2020) ⁶⁵	SABR ± hormonotherapy (n = 129) vs. conventional fractionation radiotherapy ± hormonotherapy (n = 47) Median F/U (IQR): Total: 22.9 (3.3 to 77.8) months	Age, median (range): 65 (42 to 84) years % male: 100 Primary tumour location: Prostate Met site: Multiple Number of mets: ≤ 5 Mets location: Bone or lymph node Previous tx primary tumour: Yes Previous tx mets: Unclear	NR	NR	87.7 (NR) vs. 87.3 (NR); P = 0.91	NR	NR	NR	NR	NR	NR
van de Ven et al. (2020) ⁶⁴	SABR (n = 65) vs. 3DCRT (n = 66) Median F/U (IQR): • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months	Age: 64.4 years (SABR); 68.3 years (3DCRT) % male: 51.4 Primary tumour location: Prostate, breast, lung, kidney, other (not clear in publication) Met site: Multiple Number of mets: ≤ 5 Mets location: Bone, other Previous tx primary tumour: Some patients Previous tx mets: Some patients	• 3 months: 2 vs. 5 • 6 months: 4 vs. 13 • 12 months: 6 vs. 20	85 (NR) vs. 65 (NR)	NR	NR	NR	NR	Not reached (NR) vs. 18 months (NR); P < 0.0001	0.44 (0.24 to 0.81); P = NR	NR

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadjusted HR (95% CI)	Adj HR (95% CI)
				1-year	2-year	3-year	4-year	5-year			
He et al. (2018) ⁶⁷	SABR (n = 11) vs. 3DCRT (n = 15) Median F/U: Total: 13 months	Age, median (IQR): 71 (45 to 87) years % male: 100 Primary tumour location: Colon and rectum Met site: Single Number of mets: ≤ 3 Mets location: Liver Previous tx primary tumour: Yes Previous tx mets: Some patients	NR	68.2 (NR) vs. 55.8 (NR)	40.9 (NR) vs. 16.0 (NR)	20.5 (NR) vs. 0.0 (NR)	NR	NR	20 (NR) vs. 14 (NR)	0.61 (0.23 to 1.65); P = 0.323	NR
Filippi et al. (2016) ⁶⁸	SABR (n = 28) vs. surgery (n = 142) Median F/U (IQR): • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months	Age, median (IQR): • SABR: 72.1 (66.1 to 77.0) years • Surgery: 66.4 (59.3 to 72.4) years % male: • SABR: 50 • Surgery: 61.3 Primary tumour location: Colon and rectum Met site: Single Number of mets: ≤ 5 Mets location: Lung Previous tx primary tumour: Yes Previous tx mets: For some patients	10 vs. 37	89 (70 to 96) vs. 96 (92 to 99)	77 (56 to 89) vs. 82 (74 to 87)	NR	NR	NR	NR	1.7 (0.84 to 3.43); P = 0.139	1.71 (0.82 to 3.54); P = 0.149

Study	Treatments (intervention vs. comparator); follow-up	Study characteristics	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadjusted HR (95% CI)	Adj HR (95% CI)
				1-year	2-year	3-year	4-year	5-year			
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ^{61a}	SABR (n = 42) vs. Surgery (PME) (n = 68) Short-term F/U: Median F/U (IQR) Total: 43 (36 to 60) months ⁶⁰ Long-term F/U: Median F/U (IQR) Total: 91.2 (69.6 to 117.6) months ⁶¹	Age, median (IQR): • SABR: 70 (49 to 89) years • Surgery: 61 (18 to 81) years % male: • SABR: 64.3 • Surgery: 54.4 Primary tumour location or type: Colorectal, lung sarcoma, kidney, other Met site: Single Number of mets: ≤ 5 Mets location: Lung Previous tx primary tumour: Yes Previous tx mets: For some patients	Short-term F/U: 17 vs. 35 Long-term F/U: NR	Short- and long-term F/U: 98 (84 to 100) vs. 87 (76 to 93)	Short- and long-term F/U: 86 (71 to 93) vs. 74 (61 to 82)	Short-term F/U: 60 (42 to 73) vs. 62 (49 to 73) Long-term F/U: 64 (48 to 77) vs. 63 (51 to 73)	Short-term F/U: 60 (42 to 73) vs. 47 (33 to 59) Long-term F/U: 57 (41 to 70) vs. 50 (38 to 61)	Short-term F/U: 49 (25 to 69) vs. 41 (27 to 54) Long-term F/U: 45 (30 to 59) vs. 41 (29 to 53)	Short- and long-term F/U: NR Short-term F/U: 0.79 (0.43 to 1.42); P = 0.427 Long-term F/U: 1.11 (0.70 to 1.75); P = NR; NS	Short-term F/U: NR Long-term F/U: 0.76 (0.38 to 1.54); P = NR; NS	

3DCRT = 3-dimensional conformal radiation therapy; adj = adjusted; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; met = metastasis; mets = metastases; NR = not reported; NRS = nonrandomized study; NS = non-significant; OS = overall survival; PME = pulmonary metastasectomy; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

^a OS rates at 6, 7 and 8 years for SABR vs. surgery (PME) were 35% (95% CI, 21% to 50%) vs. 37% (95% CI, 26% to 48%), 29% (95% CI, 16% to 44%) vs. 35% (95% CI, 24% to 46%), and 13% (95% CI, 3% to 30%) vs. 35% (95% CI, 24% to 46%), respectively.

Progression-Free Survival

Five studies (1 RCT,⁶³ 4 nonrandomized studies^{60,61,64,65,68}) at either high risk of bias or with some concerns of bias overall explored PFS for patients receiving SABR or SOC to treat their oligometastatic cancer (Table 11). Overall, the results were mixed: 3 studies suggested SABR provides a PFS benefit compared with SOC,⁶³⁻⁶⁵ 1 study reported SABR provides a worse prognosis in terms of PFS compared with SOC,⁶⁸ and 1 study did not provide any statistical comparison between groups.^{60,61}

One RCT compared SABR with observation in patients with previously controlled primary prostate cancer that metastasized to multiple sites (bone or soft tissue) with up to 3 oligometastases, and found a PFS benefit for the SABR group.⁶³ The unadjusted HR was 0.3 (95% CI, 0.11 to 0.81; $P = 0.002$), with a median follow-up for both arms of 18.8 (IQR, 5.8 to 35.0) months.⁶³

The nonrandomized study by Hurmuz et al.⁶⁵ found a PFS benefit of SABR with or without hormone therapy compared with conventional fractionation radiotherapy with or without hormone therapy (adjusted HR: 0.26; 95% CI, 0.13 to 0.55; $P < 0.001$; median total follow-up: 22.9; 95% CI, 3.3 to 77.8 months) in patients with previously controlled primary prostate cancer that metastasized to multiple sites (bone or lymph node or both) with up to 5 oligometastases.

The nonrandomized study by van de Ven and colleagues⁶⁴ reported a PFS benefit for SABR compared with 3DCRT in patients with multiple primary tumour locations and multiple metastatic sites with up to 5 oligometastases. The unadjusted HR was 0.63 (95% CI, 0.41 to 0.95), with a median follow-up of 25 (IQR, 5 to 52) months for the SABR group and 46 (IQR, 9 to 55) months for the 3DCRT group.⁶⁴

One nonrandomized study reported SABR provides a worse prognosis in terms of PFS compared with surgery (adjusted HR: 2.78; 95% CI, 1.67 to 4.62; $P < 0.001$) in patients with previously controlled primary colorectal cancer that metastasized to the lung with up to 5 oligometastases.⁶⁸ However, it should be noted that the study authors stated their PFS results were unreliable because different follow-up protocols were applied in the 2 cohorts.⁶⁸

Finally, another nonrandomized study compared PFS outcomes at both short- (median follow-up 43 [IQR, 36 to 60] months)⁶⁰ and long-term (91.2 [IQR, 69.6 to 117.6] months)⁶¹ follow-up time points for SABR ($n = 42$) versus surgery ($n = 68$) in patients with multiple primary tumour locations that metastasized to the lung with up to 5 oligometastases. The primary tumour in all patients had been previously treated. PFS rates provided for both groups in 1-year increments from 1 to 8 years suggested lower rates with SABR compared with surgery for metastases in the lung; however, without any statistical comparison, a conclusion could not be drawn.^{60,61} HRs were not calculated for any length of follow-up to determine the effect of SABR on PFS.^{60,61}

Table 11: PFS Comparing SABR Versus SOC

Study	Treatments (Intervention vs. Comparator)	Study characteristics	PFS rate, % (95% CI)						Median PFS (95% CI); month	Unadjusted HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
RCTs											
Phillips et al. (2020) ⁶³	SABR (n = 36) vs. observation (n = 18) Median F/U (IQR): Total: 18.8 (5.8 to 35.0) months	Age, median (IQR): • SABR: 68 (61 to 70) years • Observation: 68 (64 to 76) years % male: 100 Primary tumour location: Prostate Met site: Multiple Number of mets: ≤ 3 Mets location: Bone or soft issue Previous tx primary tumour: Yes Previous tx mets: Unclear	19 (9.6 to 35.4) vs. 61 (38.5 to 79.6)	NR	NR	NR	NR	NR	Not reached (NR) vs. 5.8 (NR)	0.3 (0.11 to 0.81); P = 0.002	NR
Non-RCTs											
Hurmuz et al. (2020) ⁶⁵	SABR ± hormonotherapy (n = 129) vs. conventional fractionation radiotherapy ± hormonotherapy (n = 47) Median F/U (IQR): Total: 22.9 (3.3 to 77.8) months	Age, median (range): 65 (42 to 84) years % male: 100 Primary tumour location: Prostate Met site: Multiple Number of mets: ≤ 5 Mets location: Bone or lymph node or both Previous tx primary tumour: Yes Previous tx mets: Unclear	NR	86.2 (NR) vs. 54.9 (NR); P < 0.001	NR	NR	NR	NR	NR	NR	0.26 (0.13 to 0.55); P < 0.001

Study	Treatments (Intervention vs. Comparator)	Study characteristics	PFS rate, % (95% CI)						Median PFS (95% CI); month	Unadjusted HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
van de Ven et al. (2020) ⁶⁴	SABR (n = 65) vs. 3DCRT (n = 66) Median F/U (IQR): • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months	Age: • SABR: 64.4 years • 3DCRT: 68.3 years % male: 51.4 Primary tumour location: Prostate, breast, lung, kidney, other (not clear in publication) Met site: Multiple Number of mets: ≤ 5 Mets location: Bone, other Previous tx primary tumour: Some patients Previous tx mets: Some patients	NR	54 (NR) vs. 19 (NR)	NR	NR	NR	NR	12 (NR) vs. 5 (NR); P = 0.002	0.63 (0.41 to 0.95); P = NR	NR
Filippi et al. (2016) ⁶⁸	SABR; n = 28 vs. surgery; n = 142 Median F/U (IQR): • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months	Age, median (IQR): • SABR: 72.1 (66.1 to 77.0) years • Surgery: 66.4 (59.3 to 72.4) years % male: • SABR: 50 • Surgery: 61.3 Primary tumour location: Colon and rectum Met site: Single Number of mets: ≤ 5 Mets location: Lung Previous tx primary tumour: Yes Previous tx mets: For some patients	NR	NR	NR	NR	NR	NR	NR	2.44 (1.51 to 3.94); P < 0.001	2.78 (1.67 to 4.62); P < 0.001

Study	Treatments (Intervention vs. Comparator)	Study characteristics	PFS rate, % (95% CI)						Median PFS (95% CI); month	Unadjusted HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ^{61a}	SABR (n = 42) vs. surgery (PME) (n = 68) Short-term F/U Median F/U (IQR): Total: 43 (36 to 60) months ⁶⁰ Long-term F/U Median F/U (IQR) Total: 91.2 (69.6 to 117.6) months ⁶¹	Age, median (IQR): • SABR: 70 (49 to 89) years • Surgery: 61 (18 to 81) years % male: • SABR: 64.3 • Surgery: 54.4 Primary tumour location or type: Colorectal, lung, sarcoma, kidney, other Met site: Single Number of mets: ≤ 5 Mets location: Lung Previous tx primary tumour: Yes Previous tx mets: For some patients	Short- and long-term F/U: NR	Short-term F/U: 50 (34 to 64) vs. 54 (42 to 65)	Short-term F/U: 21 (9 to 35) vs. 33 (22 to 45)	Short-term F/U: 8 (2 to 22) vs. 22 (12 to 33)	Short-term F/U: 8 (2 to 22) vs. 18 (9 to 30)	Short-term F/U: NR Long-term F/U: 18 (8 to 32) vs. 20 (11 to 30)	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR

3DCRT = 3-dimensional conformal radiation therapy; adj = adjusted; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; met = metastasis; mets = metastases; NR = not reported; NRS = nonrandomized study; PFS = progression-free survival; PME = pulmonary metastasectomy; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

^aPFS rates at 6, 7, and 8 years for SABR vs. surgery (PME) for all time points were 18% (95% CI, 8% to 32%) vs. 20% (95% CI, 11% to 30%).

Freedom From Progression

None of the included studies explored freedom from progression. Consequently, no summary of evidence has been conducted.

Health-Related QoL

Two studies (1 RCT,⁶³ 1 nonrandomized study⁶⁴) with an overall high risk of bias reported no significant differences between SABR versus SOC groups in the majority of health-related QoL outcomes (Table 12).

With no quantitative data reported, the RCT by Phillips and colleagues⁶³ concluded there were no differences in Brief Pain Inventory (Short Form) scores between groups (i.e., SABR versus observation) in patients with previously controlled primary prostate cancer that metastasized to bone or soft tissue with up to 3 oligometastases.

The nonrandomized study by van de Ven et al.⁶⁴ compared SABR with 3DCRT in patients with multiple primary tumour locations and multiple metastatic sites with up to 5 oligometastases and did not find any significant differences in pain response between treatment groups. The nonrandomized study authors also assessed additional pain variables, including complete response, partial response, pain progression, responders, median duration of pain response, ongoing pain response, and re-irradiation for pain recurrence or progression. At all assessed time points (3, 6, and 12 months), no significant differences were observed between the 2 groups with the exception of responders at 12 months (i.e., complete or partial response was achieved on at least 1 of the follow-up time points: SABR: 80%, n = 8; 3DCRT: 50%, n = 13; P = 0.04) and re-irradiation for pain recurrence or progression, where significantly more patients required re-irradiation for pain recurrence or progression after 3DCRT radiation therapy compared with SABR (SABR: 5%, n = 3; 3DCRT: 33.3%, n = 22; P < 0.05). It should be noted, however, the authors of this nonrandomized study excluded all patients with no pain at baseline for the assessment of pain response, which limited the number of patients for analysis and may have amplified the effect. Moreover, no significant differences between groups were found at follow-up for any QoL subscales. The physical functioning subscale appeared to be in favour of the SABR group (52-week follow-up: P = 0.04). However, the study considered P values of less than 0.01 to be statistically significant for mixed models in the QoL analyses.⁶⁴ The median follow-up in the SABR group was 25 months (IQR, 5 to 52 months), which was notably shorter than the median follow-up of 46 months in the 3DCRT group (IQR, 9 to 55 months).⁶⁴

Table 12: Health-Related QoL Comparing SABR Versus SOC

Study	Study characteristics	Tool, follow-up, results
RCT		
Phillips et al. (2020) ⁶³	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • SABR: 68 (61 to 70) years • Observation: 68 (64 to 76) years <p>% male: 100</p> <p>Primary tumour location: Prostate</p> <p>Met site: Multiple</p> <p>Number of mets: ≤ 3</p> <p>Mets location: Bone or soft tissue</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Unclear</p>	<p>Tool: Brief Pain Inventory (Short Form)</p> <p>Median F/U (IQR): Total: 18.8 (5.8 to 35.0) months</p> <p>QoL results: “No differences in Brief Pain Inventory (Short Form) scores were observed between arms or within either arm across time.” (Data not shown.)</p>
NRS		
van de Ven et al. (2020) ⁶⁴	<p>Age:</p> <ul style="list-style-type: none"> • SABR: 64.4 years • 3DCRT: 68.3 years <p>% male: 51.4</p> <p>Primary tumour location: Prostate, breast, lung, kidney, other</p> <p>Met site: Multiple</p> <p>Number of mets: ≤ 5</p> <p>Mets location: Bone, other</p> <p>Previous tx primary tumour: Some patients</p> <p>Previous tx mets: Some patients</p>	<p>Tool or measure:</p> <ul style="list-style-type: none"> • Pain: Defined according to international consensus criteria using numeric rating scale and Brief Pain Inventory scores; pain medication and daily oral morphine equivalent based on returned QoL questionnaires or determined during follow-ups • QoL: Global, functional, and role scales • Tools: EORTC QLQ-BM22, EORTC QLQ-C15-PAL, Brief Pain Inventory, EQ-5D <p>Median F/U (IQR):</p> <ul style="list-style-type: none"> • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months <p>Pain results</p> <p>Number of patients with pain at baseline:</p> <ul style="list-style-type: none"> • SBRT (n = 38); 3DCRT (n = 57) <p>Mean (SD) numeric rating scale scores at baseline:</p> <ul style="list-style-type: none"> • SBRT: 3.0 (3.5); 3DCRT: 4.6 (3.3) <p>Pain response:</p> <ul style="list-style-type: none"> • SBRT: 84% (n = 32); 3DCRT: 81% (n = 46); P = 0.79 <p>Complete response:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 16% (n = 4); 3DCRT: 25% (n = 10); P = 0.359 • 6 months – SBRT: 34.6% (n = 9); 3DCRT: 19.4% (n = 6); P = 0.180 • 12 months – SBRT: 40% (n = 4); 3DCRT: 15.4% (n = 4); P = 0.119 <p>SBRT: 5%; 3DCRT: 33.3%; P < 0.05</p>

Study	Study characteristics	Tool, follow-up, results
		<p>Partial response:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 56% (n = 14); 3DCRT: 42.5% (n = 17) • 6 months – SBRT: 34.6% (n = 9); 3DCRT: 41.9% (n = 13) • 12 months – SBRT: 40% (n = 4); 3DCRT: 34.6% (n = 9) <p>Pain progression:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 24% (n = 6); 3DCRT: 17.5% (n = 7) • 6 months – SBRT: 11.5% (n = 3); 3DCRT: 29% (n = 9) • 12 months – SBRT: 10% (n = 1); 3DCRT: 15.4% (n = 4) <p>Intermediate responses plus stable responses:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 4.2% (n = 1); 3DCRT: 15% (n = 6) • 6 months – SBRT: 19.2% (n = 5); 3DCRT: 9.7% (n = 3) • 12 months – SBRT: 10% (n = 1); 3DCRT: 34.6% (n = 9) <p>Responders:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 72% (n = 18); 3DCRT: 67.5% (n = 27); P = 0.702 • 6 months – SBRT: 69% (n = 18); 3DCRT: 60% (n = 19); P = 0.502 • 12 months – SBRT: 80% (n = 8); 3DCRT: 50% (n = 13); P = 0.04 <p>Median duration of pain response (range):</p> <ul style="list-style-type: none"> • SBRT: 24 weeks (0 to 50); 3DCRT: 23 weeks (1 to 58); P = 0.79 <p>Ongoing pain response:</p> <ul style="list-style-type: none"> • 6 months – SBRT: 65%; 3DCRT: 61%; P = 0.79 • 12 months – SBRT: 50%; 3DCRT: 42%; P = 0.77 <p>Re-irradiation for pain recurrence or progression:</p> <p>QoL results (where P values of < 0.01 were considered statistically significant for mixed models):</p> <ul style="list-style-type: none"> • No significant differences between groups for any QoL subscales.

3DCRT = 3-dimensional conformal radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Bone Metastasis 22; EORTC QLQ-C15-PAL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative; EQ-5D = EuroQol 5-Dimensions questionnaire; FACT-G = Functional Assessment of Cancer Therapy-General; F/U = follow-up; IQR = interquartile range; met = metastasis; mets = metastases; NRS = nonrandomized study; QoL = quality of life; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiotherapy; SOC = standard of care; tx = treatment.

Table 13: Lesional Control Comparing SABR Versus SOC

Study	Treatments (intervention vs. comparator)	Study characteristics	LC rate, % (95% CI) SABR vs. surgery						Median LC (95% CI); months	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
			1-year	2-year	3-year	4-year	5-year	6-year			
NRSs											
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ^{a,61}	SABR (n = 42) vs. surgery (PME) (n = 68) Short-term F/U Median F/U (IQR): • Total: 43 (36 to 60) months ⁶⁰ Long-term F/U Median F/U (IQR): • Total: 91.2 (69.6 to 117.6) months ⁶¹	Age, median (IQR): • SABR: 70 (49 to 89) years • Surgery: 61 (18 to 81) years % male: • SABR: 64.3 • Surgery: 54.4 Primary tumour location or type: Colorectal, sarcoma, lung, kidney, other Met site: Single Number of mets: ≤ 5 Mets location: Lung Previous tx primary tumour: Yes Previous tx mets: For some patients	Short-term F/U: 94 (79 to 99) vs. 93 (83 to 97)	Short-term F/U: 94 (79 to 99) vs. 90 (78 to 96)	Short-term F/U: 85 (55 to 96) vs. 83 (65 to 92)	Short-term F/U: 85 (55 to 96) vs. 83 (65 to 92)	Short-term F/U: NR Long-term F/U: 83 (57 to 94) vs. 81 (65 to 90)	Short-term F/U: NR Long-term F/U: 83 (57 to 94) vs. 81 (65 to 90)	Short- and long-term F/U: NR Long-term F/U: 0.8 (0.24 to 2.65)	Short- and long-term F/U: NR	

adj = adjusted; CI = confidence interval; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; LC = lesional control; met = metastasis; mets = metastases; NR = not reported; NRS = nonrandomized study; PME = pulmonary metastasectomy; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

^aRate of LC at 7 and 8 years for SABR and surgery (PME) at both time points was 83% (95% CI, 57% to 94%) vs. 81% (95% CI, 65% to 90).

Lesional Control

One nonrandomized study (from 2 publications)^{60,61} with an overall high risk of bias explored LC outcomes (Table 13). The study compared LC outcomes at both short- and long-term follow-up time points between SABR (n = 42) and surgery (n = 68) in patients with multiple primary tumour locations that metastasized to the lung with up to 5 oligometastases. The primary tumour in all patients had been previously treated. The median short-term follow-up was 43 (IQR, 36 to 60) months⁶⁰ and the median long-term follow-up was 91.2 (IQR, 69.6 to 117.6) months.⁶¹ LC rates in 1-year increments from 1 to 8 years were numerically comparable between groups, without any statistical comparison. An unadjusted HR was calculated at long-term follow-up, which found no significant differences between groups; the unadjusted HR was 0.8 (95% CI, 0.24 to 2.65).⁶¹

Systemic Therapy Use

None of the included studies explored systemic therapy use after treatment with SABR; consequently, no summary of evidence has been conducted.

Question 2: Safety**SABR With SOC Versus SOC*****Adverse Events***

Two RCTs (from 3 publications)^{32,58,69} at either high risk of bias or with some concerns of bias overall monitored toxicity for patients who received either SABR plus SOC or SOC alone to treat their oligometastatic cancer (Table 14). Both studies used the CTCAE version 4.0 tool to assess AEs.^{32,58,69} Overall, it is unclear if there is a difference in AE incidence when comparing SABR with SOC to SOC alone.

Iyengar et al.⁶⁹ compared SABR plus maintenance chemotherapy to maintenance chemotherapy alone in patients with a controlled primary lung tumour that metastasized to multiple locations with up to 5 oligometastases. This study provided AE frequencies for each group, separated according to AE grade, but did not report statistical findings. Despite this, the study authors concluded there were no differences in toxic effects between groups.⁶⁹

The SABR-COMET RCT in 2 publications^{32,58} compared SABR plus systemic therapy to systemic therapy alone in patients with controlled primary tumours in multiple locations that metastasized to multiple sites with up to 5 oligometastases. Various toxicity comparisons were presented, including AEs (grade 2 or greater), treatment-related AEs (grade 2 or greater), death (grade 5), fatigue (grade 2 and grade 3), dyspnea (grade 2 and grade 3), and pain (grade 2 [any type, including muscle, bone, and other] and grade 3 [any type]). Results from SABR-COMET^{32,58} revealed that SABR plus systemic therapy was associated with a significantly higher rate of related AEs of grade 2 or greater compared with systemic therapy alone (29% versus 9%; P = 0.026), with an absolute increase of 20% (95% CI, 5 to 34). For all other AE comparisons, no significant differences between groups were found.^{32,58}

Table 14: Adverse Events Comparing SABR With SOC Versus SOC

Study	Study characteristics	Tool, follow-up, results
SABR-COMET Palma et al. (2019), ³² Palma et al. (2020) ⁵⁸	Age, median (IQR): <ul style="list-style-type: none"> • SABR + SOC: 66.8 (42.8 to 89.4) years • SOC: 68.6 (44.2 to 87.0) years % male: <ul style="list-style-type: none"> • SABR + SOC: 61 • SOC: 58 Primary tumour location: Breast, colorectal, lung, prostate, and other (not described in publication) Met site: Multiple Number of mets: ≤ 5 Mets location: Adrenal, bone, liver, lung, other: <ul style="list-style-type: none"> • brain (3 lesions in control; 1 lesion in SABR + SOC) • lymph nodes (1 lesion in control; 3 lesions in SABR + SOC) • para-renal (1 in SOC) Previous tx primary tumour: Yes Previous tx mets: Yes	RCTs Tool used to assess toxicity: CTCAE v4.0 Short-term F/U Median F/U (IQR) – SABR + SOC: 26 (23 to 37) months; SOC: 25 (19 to 54) months ³² Long-term F/U Median F/U (IQR) – Total: 51 (46 to 58) months ⁵⁸ Results: Number of patients with AEs AE grade ≥ 2: <ul style="list-style-type: none"> • SABR + SOC: 61% (n = 40) vs. SOC: 46% (n = 15); P = 0.15 Treatment-related AE grade ≥ 2: <ul style="list-style-type: none"> • SABR + SOC: 29% (n = 19) vs. SOC: 9% (n = 3); P = 0.026 with an absolute increase of 20% (95% CI, 5 to 34) Death (grade 5): <ul style="list-style-type: none"> • SABR + SOC: 4.5% (n = 3; radiation pneumonitis [n = 1], pulmonary abscess [n = 1], and subdural hemorrhage after surgery to repair a SABR-related perforated gastric ulcer [n = 1]) vs. SOC: 0% (n = 0); P = 0.55 Fatigue (grade 2): <ul style="list-style-type: none"> • SABR + SOC: 6% (n = 4) vs. SOC: 6% (n = 2); P = 0.45 Fatigue (grade 3): <ul style="list-style-type: none"> • SABR + SOC: 0% (n = 0) vs. SOC: 3% (n = 1); P = 0.45 Dyspnea (grade 2): <ul style="list-style-type: none"> • SABR + SOC: 2% (n = 1) vs. SOC: 0% (n = 0); P = 1.00 Dyspnea (grade 3): <ul style="list-style-type: none"> • SABR + SOC: 2% (n = 1) vs. SOC: 0% (n = 0); P = 1.00 Pain (any type, including muscle, bone, and other; grade 2) <ul style="list-style-type: none"> • SABR + SOC: 8% (n = 5) vs. SOC: 0% (n = 0); P = 0.14 Pain (any type, including muscle, bone, and other; grade 3) <ul style="list-style-type: none"> • SABR + SOC: 5% (n = 3) vs. SOC: 0% (n = 0); P = 0.14

Study	Study characteristics	Tool, follow-up, results
lyengar et al. (2018) ⁶⁹	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • SABR + maintenance chemotherapy: 63.5 (51.0 to 78.0 years) • Maintenance chemotherapy: 70.0 (51.0 to 79.0) years <p>% male:</p> <ul style="list-style-type: none"> • SABR + maintenance chemotherapy: 64.3 • Maintenance chemotherapy: 73.3 <p>Primary tumour location: Lung</p> <p>Met site: Multiple</p> <p>Number of mets: ≤ 5</p> <p>Mets location: Lung, adrenal, mediastinum, axilla, liver, nasopharynx, bone (rib, spine)</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Yes</p>	<p>Tool used to assess toxicity:</p> <p>CTCAE v4.0</p> <p>Median F/U (IQR)</p> <p>Total: 9.6 (2.4 to 30.2) months</p> <p>Toxicity results (number of events):</p> <ul style="list-style-type: none"> • Grade 1 – SABR + maintenance: 13 vs. maintenance only: 17 • Grade 2 – SABR + maintenance: 5 vs. maintenance only: 5 • Grade 3 – SABR + maintenance: 4 vs. maintenance only: 2 • Grade 4 – SABR + maintenance: 0 vs. maintenance only: 1 • Grade 5 – SABR + maintenance: 3 vs. maintenance only: 6

AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; IQR = interquartile range; met = metastasis; mets = metastases; NR = not reported; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SOC = standard of care; tx = treatment; vs. = versus.

SABR Versus SOC

Adverse Events

Four studies (1 RCT,⁶³ 3 nonrandomized studies⁶⁶⁻⁶⁸) at a high risk of bias or with some concerns of bias overall monitored toxicity for patients who received either SABR or SOC to treat their oligometastatic cancer (Table 15). The majority of studies used the CTCAE^{63,66-68} or RTOG grading system^{66,67} to assess AEs. Overall, it is unclear if there is a difference in AE incidence when comparing SABR with SOC.

One RCT by Phillips et al. reported a larger number of grade 1 and 2 AEs at both 90-day and 180-day time points for the SABR group versus observation.⁶³ Patients in this trial had controlled primary prostate cancer that metastasized to the bone or soft tissue with up to 3 oligometastases.

One nonrandomized study by De Bleser et al.⁶⁶ compared SABR with or without ADT to ENRT with or without ADT in patients with controlled primary prostate cancer that metastasized to pelvic and extra-pelvic lymph nodes with up to 5 oligometastases. Three toxicity comparisons were presented, including early toxicity (all grades), late toxicity (all grades), and early and late toxicity (grade 3 or higher).⁶⁶ Compared with ENRT, SABR was associated with a lower rate of AEs for all 3 comparisons ($P < 0.05$; median follow-up for both arms: 18.8 months; IQR, 5.8 to 35.0 months).⁶⁶

One nonrandomized study by He et al.⁶⁷ compared SABR with 3DCRT in patients with controlled primary colorectal cancer that metastasized to the liver with up to 3 oligometastases. The study found no differences between groups for the hepatic toxicity-inducing rate, though specific rates per group were not reported ($P = 0.674$). Between-group

differences were descriptively reported for liver toxicity: the SABR group had 1 patient with a grade 1 or 2 AE and 1 patient with a grade 3 AE, and the 3DCRT group had 3 patients with a grade 1 or 2 AE and 2 patients with a grade 3 AE.⁶⁷

One nonrandomized study by Filippi et al.⁶⁸ did not conduct statistical testing to evaluate AEs with SABR compared with SOC. The study reported specific AEs with the number and proportion of patients in each grade, which precludes suitable comparison between groups; however, the study authors reported the SABR group had multiple grade 1 to 3 AEs and the surgery group reported 1 death. Patients in this study had primary colorectal cancer that metastasized to the lung with up to 5 oligometastases.

Table 15: Adverse Events Comparing SABR Versus SOC

Study	Study characteristics	Tool, follow-up, results
RCTs		
Phillips et al. (2020) ⁶³	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • SABR: 68 (61 to 70 years) • Observation: 68 (64 to 76 years) <p>% male: 100</p> <p>Primary tumour location: Prostate</p> <p>Met site: Multiple</p> <p>Number of mets: ≤ 3</p> <p>Mets location: Bone or soft issue</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Unclear</p>	<p>Tool used to assess toxicity: CTCAE v4.0</p> <p>Median follow-up (IQR): Total: 36 (23 to 56) months</p> <p>Results: Number of patients with AEs</p> <p>New grade 1 AEs at 90 days:</p> <ul style="list-style-type: none"> • SABR: 29/36 (81%) versus observation: 12/16 (75%) <p>New grade 1 AEs at 180 days:</p> <ul style="list-style-type: none"> • SABR: 15/36 (42%) versus observation: 3/11 (27%) <p>New grade 2 AEs at 90 days:</p> <ul style="list-style-type: none"> • SABR: 3/36 (8%) versus observation: 0/16 (0) <p>New grade 2 AEs at 180 days:</p> <ul style="list-style-type: none"> • SABR: 2/36 (6%) versus observation: 0/11 (0) <p>Grade 3 or higher:</p> <ul style="list-style-type: none"> • None
NRSS		
De Bleser et al. (2019) ⁶⁶	<p>Age (median, IQR):</p> <ul style="list-style-type: none"> • SABR: 63 (58 to 68) years • ENRT: 63 (59 to 68) years <p>% male: 100</p> <p>Primary tumour location: Prostate</p> <p>Met site: Multiple</p> <p>Number of mets: ≤ 5</p> <p>Mets location: Pelvic and extra-pelvic lymph nodes</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Some patients</p>	<p>Tool used to assess toxicity: CTCAE or RTOG grading system</p> <p>Median F/U (IQR): Total: 18.8 (5.8 to 35.0) months.</p> <p>Results: Number of patients with AEs</p> <p>Grade 3 or higher in both early and late toxicity</p> <ul style="list-style-type: none"> • SABR: 0 (0%) • ENRT: 5 (2.5%); P = 0.009 <p>Early toxicity of all grades:</p> <ul style="list-style-type: none"> • SABR: 3 (1%) • ENRT: 12 (6%); P = 0.002 <p>Late toxicity of all grades:</p> <ul style="list-style-type: none"> • SABR: 16 (5%) • ENRT: 31 (16%); P < 0.001

Study	Study characteristics	Tool, follow-up, results
He et al. (2018) ⁶⁷	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • 71 (45 to 87) years <p>% male: 100</p> <p>Primary tumour location: Colon and rectum</p> <p>Met site: Single</p> <p>Number of mets: ≤ 3</p> <p>Mets location: Liver</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: Some patients</p>	<p>Tool used to assess toxicity:</p> <p>CTCAE v3.0 or RTOG</p> <p>Median F/U:</p> <p>Total: 13 months</p> <p>Liver toxicity results:</p> <ul style="list-style-type: none"> • SABR: One patient had grade 1 to 2; 1 patient had grade 3 • 3DCRT: Three patients had grade 1 and 2; 2 patients had grade 3 <p>Hepatic toxicity-inducing rate:</p> <ul style="list-style-type: none"> • No difference between groups (P = 0.674)
Filippi et al. (2016) ⁶⁸	<p>Age, median (IQR):</p> <ul style="list-style-type: none"> • SABR: 72.1 (66.1 to 77.0) years • Surgery: 66.4 (59.3 to 72.4) years <p>% male:</p> <ul style="list-style-type: none"> • SABR: 50 • Surgery: 61.3 <p>Primary tumour location: Colon and rectum</p> <p>Met site: Single</p> <p>Number of mets: ≤ 5</p> <p>Mets location: Lung</p> <p>Previous tx primary tumour: Yes</p> <p>Previous tx mets: For some patients</p>	<p>Tool used to assess toxicity:</p> <p>CTCAE v3.0</p> <p>Median F/U (IQR):</p> <ul style="list-style-type: none"> • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months <p>Results:</p> <p>SABR:</p> <ul style="list-style-type: none"> • Pulmonary toxicity – grade 0: 64.2% (n = 18); grade 1: 21.4% (n = 6); grade 2: 14.4% (n = 4) • Radiological lung toxicity – grade 0: 39.2% (n = 11); grade 1: 17.8% (n = 5); grade 2: 28.6% (n = 8); grade 3: 14.4% (n = 4) • Chronic chest wall pain – grade 2: 3.6% (n = 1); grade 3: 3.6% (n = 1) • Skin toxicity – grade 2: 3.6% (n = 1) <p>Surgery:</p> <ul style="list-style-type: none"> • Death: 0.7% (n = 1) within 30 days

3DCRT = 3-dimensional conformal radiation therapy; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ENRT = elective nodal radiotherapy; F/U = follow-up; IQR = interquartile range; met = metastasis; mets = metastases; NRS = nonrandomized study; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; RTOG = Radiation Therapy Oncology Group; tx = treatment.

Patient Engagement

A patient collaborator was involved in the development of this project, from discussing the research question and outcomes in the protocol, to commenting on the draft findings, to being invited to provide feedback on the baseline clinical review.

The involvement of a patient collaborator enabled the research team to consider the evidence along with the wider experiences of patients and families when preparing the assessment. A deep discussion of clinical outcomes, particularly OS, PFS, and health-related QoL, revealed the goals of treatment with SABR. In CADTH's conversations with the patient collaborator, the outcome that was discussed most by the patient was health-related QoL, including pain and fatigue, indicating the importance of remaining active and being able to return to work after treatment. The patient compared and contrasted the experience of having chemotherapy to

treat the primary tumour versus SABR to treat the metastatic site and highlighted that SABR provided improved health-related QoL outcomes. A description of the patient collaborator's rural location and distance to travel for treatment was noted. Patient group stakeholders (Canadian Partnership Against Cancer and Canadian Cancer Survivors Network) were invited to provide feedback on the clarity and relevance of the draft of the baseline clinical review.

Patient involvement was guided by the GRIPP2-SF reporting checklist and is reported in Table 25.⁵⁵

Summary of Results

Three RCTs (from 5 publications^{32,58,59,62,63}) and 6 nonrandomized studies (from 7 publications^{60,61,64-68}) were identified that compared SABR alone or in combination with other SOC therapies with SOC alone for the treatment of patients with oligometastatic cancer. All 9 studies reported on clinical effectiveness. Three RCTs and 3 nonrandomized studies reported on AEs. For the included studies, SOC interventions comprised surgery, conventional radiotherapy, systemic therapy (i.e., chemotherapy, hormone therapy, ADT), or no therapy (i.e., observation). The studies were grouped into 2 main comparisons (i.e., SABR with SOC versus SOC alone and SABR versus SOC). Key findings were narratively synthesized; no meta-analyses were conducted.

Regarding the clinical effectiveness of SABR plus SOC versus SOC alone, 2 RCTs (from 3 publications)^{32,58,69} provided some evidence that SABR plus SOC might be associated with OS and PFS benefits compared with SOC alone. The overall risk of bias of these studies was either high or with some concerns. Results from SABR-COMET^{32,58} showed longer median OS and lower HRs for OS in the SABR plus systemic therapy group, compared with systemic therapy alone, in both short- and long-term follow-ups. Likewise, the results from the Iyengar et al. RCT⁶⁹ also suggested longer median OS in the SABR plus maintenance chemotherapy group compared with the maintenance chemotherapy alone group. Consistently, the available PFS data from 2 RCTs^{58,69,71} suggest that SABR plus SOC provides a significant PFS benefit compared with SOC alone. Considering patients with oligometastases have already had progression of their cancer via metastases, benefits in PFS may be of particular importance to this population; CADTH's patient collaborator agreed with this suggestion. In terms of health-related QoL, 1 RCT found no significant differences between SABR plus systemic therapy versus systemic therapy alone in the overall mean of the FACT-G scores, or in any of the physical, social, functional, or emotional subscales.^{58,59} In terms of LC, 1 RCT^{32,58} found improved crude rates for SABR plus systemic therapy compared with systemic therapy alone in both the shorter- and longer-term follow-ups. The paucity of available evidence for health-related QoL and LC makes it difficult to provide definitive conclusions for those outcomes. None of the included studies explored freedom-from-progression outcomes or subsequent systemic therapy use.

Seven studies, comprising 1 RCT⁶³ and 6 nonrandomized studies (from 7 publications),^{60,61,64-68} explored the clinical effectiveness of SABR versus SOC. The overall risk of bias of these studies was either high or with some concerns. The SOC comparator varied widely between studies and was dependent on the type of cancer being treated. SOC comparators included observation,⁶³ 3DCRT,^{64,65,67} conventional fractionation radiotherapy with or without hormone therapy,⁶⁵ ENRT with or without ADT,⁶⁶ and surgery (various resections, pulmonary metastasectomy).^{60,61,68} Consideration for these differences in the comparator is warranted when interpreting the following narrative findings.

Five nonrandomized studies^{60,61,64,65,67,68} provided evidence suggesting that SABR may not be more effective than SOC for OS. Specifically, 1 nonrandomized study⁶⁴ found that SABR was associated with a significantly longer median OS than 3DCRT, despite the shorter follow-up in the SABR group; however, the study authors attributed the OS benefit largely to selection bias demonstrated by imbalances in baseline characteristics between the 2 groups. The remaining 4 nonrandomized studies^{60,61,65,67,68} did not find significant differences in OS between SABR and SOC. Most of the nonrandomized studies likely suffered from several limitations, such as incomplete control for confounding factors, immaturity in data, selection of patients as shown by differences in baseline characteristics between treatment groups, lack of power, and imbalances in sample sizes and differences in follow-up protocols between treatment groups. These preliminary findings from nonrandomized studies with potential limitations precluded a definitive conclusion regarding the clinical benefit of SABR alone compared with SOC alone in improving OS for patients with oligometastatic cancer.

In terms of PFS, 5 studies (1 RCT⁶³ and 4 nonrandomized studies^{60,61,64,65,68}) provided mixed results when comparing SABR with SOC. Three studies (1 RCT⁶³ and 2 nonrandomized studies^{64,65}) suggested SABR provided a PFS benefit compared with SOC alone (i.e., observation, hormone therapy, or radiotherapy), 1 nonrandomized study⁶⁸ suggested that SABR provided a worse prognosis in terms of PFS compared with surgery, and 1 nonrandomized study^{60,61} did not find any significant differences between SABR and surgery. Several of the limitations for OS in the nonrandomized studies indicated previously might also apply to PFS and, since PFS data do not always correlate with OS,⁷² the overall findings of PFS in the comparison of SABR versus SOC should be interpreted with caution. One RCT⁶³ and 1 nonrandomized study⁶⁴ explored health-related QoL outcomes and found no significant differences between groups (i.e., SABR versus observation,⁶³ SABR versus 3DCRT⁶⁴) in the majority of health-related QoL outcomes. One nonrandomized study (from 2 publications)^{60,61} investigated LC and found no differences in LC rates between SABR and pulmonary metastasectomy surgery at both short- and long-term follow-ups.^{60,61} None of the included studies explored outcomes related to freedom from progression or systemic therapy use.

The second clinical research question for this review aimed to determine the safety of SABR alone or in combination with other therapies for the treatment of patients with oligometastatic cancer compared with SOC alone. Results were narratively summarized by comparison (i.e., SABR plus SOC versus SOC alone, SABR versus SOC).

Two RCTs (from 3 publications)^{32,58,69} explored AEs for patients who received SABR plus systemic therapy or systemic therapy alone. For the SABR-COMET trial,^{32,58} SABR plus systemic therapy was associated with a significantly higher rate of treatment-related AEs of grade 2 or greater, without any significant differences for all other AE comparisons. The trial by Iyengar and colleagues⁶⁹ did not statistically compare the AEs experienced by patients, but the study authors concluded there were no differences in toxic effects between SABR plus maintenance chemotherapy and maintenance chemotherapy alone.

Four studies (1 RCT,⁶³ 3 nonrandomized studies⁶⁶⁻⁶⁸) provided unclear evidence on whether SABR reduces AE incidence compared with SOC (i.e., observation, radiotherapy, or surgery). Two studies^{60,63,68} did not conduct statistical testing to determine whether rates of AEs were different between SABR and SOC groups. The nonrandomized study that explored SABR with or without ADT versus ENRT with or without ADT⁶⁶ found that SABR was associated with a lower rate of AEs compared with ENRT. Finally, the nonrandomized study that compared SABR with 3DCRT⁶⁷ did not find significant differences in hepatic toxicity-inducing rates between groups.

Discussion

Generalizability of Findings

This clinical review explores the clinical effectiveness and safety of SABR for any patients with oligometastatic cancer. There is currently no standardized definition of the oligometastatic state; therefore, CADTH used a definition for oligometastatic cancer informed by clinical experts and solicited stakeholder feedback on the included studies list for this review. For the purposes of this review, the population of interest was patients with oligometastatic cancer, described by study authors as having limited metastatic lesions using terminology such as “oligo,” “limited,” or “few,” including identification of de novo or repeat oligometastatic disease at any time during the patient’s course of treatment, irrespective of the status of the primary tumour. However, this definition may have excluded studies that other research groups may have deemed to involve oligometastatic cancer that did not meet our definition, and the results of this review may not be applicable to every interpretation of “oligometastatic cancer.” On the other hand, the other inclusion criteria were quite broad and allowed for the inclusion of diverse patient populations within the oligometastatic disease spectrum; comparative studies examining SABR for patients with oligometastatic cancer were included regardless of the location of primary tumour, location of metastases, number of metastases, or number of metastatic sites. This review excluded studies involving patients who had a history of widespread metastatic disease (i.e., induced oligometastatic disease); however, it is possible that a study included “oligometastatic” patients without additional information regarding previous widespread disease. For this review, it was assumed that patients had no history of widespread metastatic disease if this was not explicitly described in the study; in those cases, the studies may have included patients with a history of widespread metastatic disease that were unknowingly included in this review.

Oligometastatic disease is an umbrella term in the sense that patients can have different types of primary and metastatic location combinations and may have different clinical profiles. Different primary cancer types have different disease prognoses, making it difficult to assess transferability of findings between patient populations. This review did not identify any subgroup analysis for the subgroups of interest. Nevertheless, some of the findings were specific to primary lung cancer⁶⁹ or primary prostate cancer,^{65,66} including up to 3 metastases,^{63,67} multiple metastatic sites^{32,58,59,63-66,69} or a single metastatic site such as lung^{60,61,68} or liver,⁶⁷ patients with previous treatment of a primary tumour,^{32,58-61,63,65-68} or patients with previous treatment of metastases.^{32,58-61,64,66-69} In addition, while patients of any age were of interest for this review, all included studies evaluated adult patients, with a median age above 60 years in all treatment groups. Therefore, the results may not be applicable to pediatric patients or to younger adults with oligometastatic cancer.

For this review, 1 RCT (from 3 publications)^{32,58,59} was conducted at multiple institutions across Canada, the Netherlands, UK, and Australia. The remaining 8 studies⁶⁰⁻⁶⁸ were conducted outside of Canada. However, the majority of the evidence was from developed countries and, therefore, may be generalizable to the Canadian context.

CADTH engaged 1 patient with lived experience of oligometastatic cancer to inform the selection of important clinical outcomes and to provide the reviewers with some context for interpretation of the findings. The purpose of patient engagement is not to be representative of all Canadians, recognizing that individual patients have a diversity of experiences and perceptions related to oligometastatic cancer and its treatment. Comments and perspectives

from our patient collaborator were not analyzed; rather, CADTH drew on patient perspectives and impressions to help better inform the work and help interpret the clinical evidence. Of note, the topic and research questions were already determined before engaging the patient collaborator. Possible limitations of this patient engagement were that our collaborator and other patient stakeholders were invited to participate within a set time frame and with a deadline for providing feedback. People need access to reliable technology and phone and internet service to participate; lack of such access could possibly exclude some voices.

Limitations

There are certain limitations to consider when reviewing the report, which are described subsequently.

Evidence Gaps

There were a number of gaps in the evidence identified for this review. Namely, there were relatively few studies identified for each intervention and comparator combination; 3 studies (2 RCTs^{32,58,59,69}) evaluated SABR plus SOC versus SOC alone, and 8 studies (1 RCT⁶³ and 7 nonrandomized studies^{60,61,64-68,70}) evaluated SABR versus SOC. Within those comparison categories, the outcomes of interest for this review were often not reported by all of the included studies, further reducing the available evidence for comparison. Evidence for the AE outcomes in particular was very limited due to how the data were recorded (e.g., treatment-related versus non-treatment-related AEs, event data versus patient data, only selective grades reported). No data were identified from any study to report on freedom from progression and subsequent use of systemic therapy. In addition, subgroup analyses within studies were lacking; instead, studies were described with relevant patient characteristics only when presenting overall study results. There was no evidence identified to comment on the effectiveness or safety of SABR based on patient age, sex, or gender.

To be comprehensive, this review used broad inclusion criteria for SOC for metastatic cancer, which varies according to the type of primary cancer and metastatic site. This variety is reflected in the wide range of SOC comparators described in the included studies, which were narratively synthesized in the same manner without discerning the efficacy of 1 comparator over another (e.g., surgery versus observation). In addition, several studies broadly included patients with oligometastatic cancer that included multiple types of primary cancers and locations of oligometastases without presenting subgroup analyses of results by primary tumour or oligometastatic location. While results in the present work compare SABR with any type of SOC deemed appropriate for patients of a certain variation of oligometastatic cancer, there was not enough evidence identified in this review to truly discern whether certain cancer types or intervention combinations may benefit from SABR more than others. Similarly, the dose used when administering SABR was study-dependent and varied based on the protocol used in consideration of the location(s) of the targeted metastatic site(s), the frequency and number of fractions per lesion per patient, and complication risks to nearby normal tissue. Clinical experts engaged by CADTH have suggested that this is consistent with their experience in practice. Furthermore, the relationship between the size of the lesion(s) and dose may affect patient outcomes. For example, treating larger lesions may be associated with higher toxicities from treatment, and lower LC rates may be observed in situations where lower-dose prescriptions are used for patient safety. CADTH is unable to provide details on the optimal SABR regimen or dose, given the variation in the included studies. As SABR dose is dependent on many factors, it may be challenging to identify optimal SABR regimens or standardized doses that could be applicable across all oligometastatic cancers or patients.

Taken together, the limited amount of evidence identified combined with the variation in patient characteristics and outcome reporting across and within the included studies affected the ability to quantitatively synthesize findings and reflects a high degree of uncertainty in the findings to date. For this review, 9 studies (from 12 publications) were included. A 2019 paper identified 64 ongoing studies examining SABR for oligometastatic cancer.³³ CADTH's detailed scoping exercise and additional grey literature searches also identified a number of ongoing clinical trials.¹ Thus, there is undoubtedly more evidence coming down the research pipeline in the near future that will likely add to our current evidence base to inform whether SABR should be used for patients with oligometastatic cancer and under what conditions (e.g., patient characteristics, dose). Regular updates of this baseline review are planned to capture additional and relevant studies in the form of a LSR.

Heterogeneity

There was substantial clinical, methodological, and statistical heterogeneity among the included studies preventing meta-analyses of the data. Specifically, sources of heterogeneity included differences in study design (i.e., RCT, nonrandomized study), data unavailability (e.g., 2 relevant studies for the comparison of interest, but HRs reported for 1 study), data variability (e.g., AE results included different AE grades reported, treatment-related versus non-treatment-related AEs, or event data versus patient data), and discordant results (i.e., large variability in the direction, magnitude, and statistical significance of the results). As discussed previously, there was variation in the patient characteristics within and across included studies (e.g., type of primary tumour, location of oligometastases) and types of treatment comprising SOC that contributed to the heterogeneity, which is also reflected by the inconsistent results in the narrative synthesis for some comparisons and outcomes.

Quality of Evidence

The included studies comprised both RCTs and nonrandomized studies (with the majority using a retrospective cohort study design). The risk of bias of the included studies ranged from high risk of bias to some concerns. All included RCTs were phase II trials with limitations in the randomization process and with relatively small sample sizes, although power calculations were performed. All of the included nonrandomized studies were susceptible to the risk of selection bias, reporting bias, and lack of power calculations. For feasibility reasons, only studies published in English were eligible for inclusion. It is acknowledged that there is a potential for language bias when language restrictions are used; however, there is also evidence for minimal impact of including studies published in other languages.^{73,74}

Directions for Future Research

In order to facilitate decisions around appropriate patient selection and the optimal SABR regimen or dose, additional studies examining the clinical effectiveness and safety of SABR with detailed reporting of criteria for patient selection and dosing are required. Additional studies examining any clinical outcomes outlined in this review may also enable future meta-analyses of the data to provide more robust findings, as several of the comparisons could not be pooled due to the lack of available evidence (i.e., no HRs to pool). Specifically, the patient partner emphasized QoL as 1 of the central outcomes of interest, including breathing issues, fatigue, impact on physical activity, and being able to return to work after treatment. Some evidence was available regarding QoL (3 studies), mainly focusing on pain and less on physical functioning. Additional research regarding the interventions' impact on QoL is warranted. Moreover, the patient collaborator described the distance to travel for treatment and the costs associated with travel, highlighting some practical considerations related to

accessing SABR treatment. As SABR for the treatment of oligometastatic cancer is an active field of research, additional studies are expected to be identified upon updates of this baseline review during the LSR phase. Such updates may provide an opportunity to fill in gaps in the clinical evidence and strengthen the conclusions of this review.

Conclusions and Implications for Decision-Making

To CADTH's knowledge, this is the first systematic review exploring the clinical effectiveness and safety of SABR for any patients with oligometastatic cancer (i.e., no restrictions on primary or metastatic locations). Key outcomes of interest included OS, PFS, and AEs, consistent with the opinions of our clinical experts and patient partner. Findings from the included studies suggested there may be OS and PFS benefits associated with SABR plus SOC compared with SOC alone. Findings from the included studies on OS and PFS for SABR alone versus SOC were mixed and deemed inconclusive, as the studies were generally limited by unadjusted baseline imbalances associated with the retrospective cohort study design and suffered from small sample sizes and uncertainty around whether the survival data were mature. Few studies statistically compared AE data, making it unclear if SABR, with or without SOC, is more or less harmful than SOC alternatives for patients with oligometastases. There was a lack of literature identified to inform conclusions for other outcomes of interest, including freedom from progression, health-related QoL, LC, and use of systemic therapy after treatment, and for subgroups of interest (i.e., age, sex, gender, location of primary tumour site, number of metastases sites, number of metastases, location of metastases, previous treatment of primary tumour, and previous treatment of metastases). More comparative studies using rigorous methods, such as high-quality randomized trials with sufficient sample sizes and mature OS data, are required to reduce this uncertainty. Future research on the effectiveness of SABR in patients with different characteristics would clarify who might benefit most from this treatment, which would inform patient selection criteria. In addition, evidence on the optimal regimen or dose of SABR for treatment of oligometastases is still needed. Additional studies are expected to be identified during the LSR phase of this project, which will see routine monitoring for newly published literature and regular updating of this baseline review. Finally, this clinical review represents 1 component among many that decision-makers will consider when making the decision about the expanded use of SABR in Canada.

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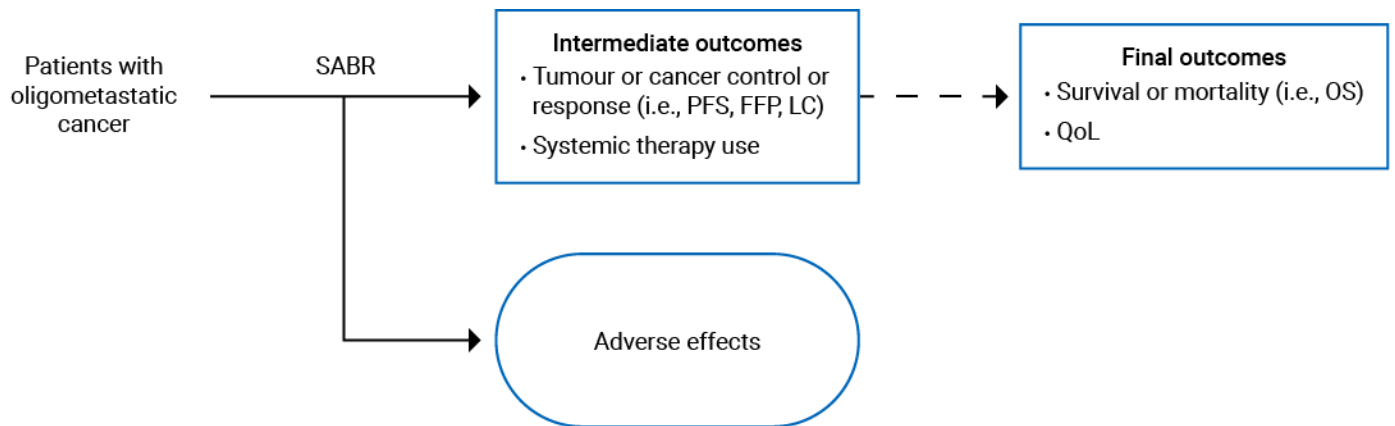
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59. Olson R, Senan S, Harrow S, et al. Quality of Life Outcomes After Stereotactic Ablative Radiation Therapy (SABR) Versus Standard of Care Treatments in the Oligometastatic Setting: A Secondary Analysis of the SABR-COMET Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2019;105(5):943-947.
60. Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? *Radiother Oncol*. 2013;107(3):409-413.
61. Lodeweges JE, Klinkenberg TJ, Ubbels JF, Groen HJM, Langendijk JA, Widder J. Long-term Outcome of Surgery or Stereotactic Radiotherapy for Lung Oligometastases. *J Thorac Oncol*. 2017;12(9):1442-1445.
62. Iyengar P, Tumati V, Gerber D, et al. Consolidative radiotherapy for limited metastatic non-small cell lung cancer: A randomized phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2017;99(5):1314.
63. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(5):650-659.
64. van de Ven S, van den Bongard D, Pielkenrood B, et al. Patient-Reported Outcomes of Oligometastatic Patients After Conventional or Stereotactic Radiation Therapy to Bone Metastases: An Analysis of the PRESENT Cohort. *Int J Radiat Oncol Biol Phys*. 2020;30:30.
65. Hurmuz P, Onal C, Ozyigit G, et al. Treatment outcomes of metastasis-directed treatment using (68)Ga-PSMA-PET/CT for oligometastatic or oligorecurrent prostate cancer: Turkish Society for Radiation Oncology group study (TROD 09-002). *Strahlenther Onkol*. 2020;196(11):1034-1043.
66. De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol*. 2019;76(6):732-739.
67. He Z, Chen G, Ouyang B, et al. Conformal radiation therapy or stereotactic body radiation therapy: Institutional experience in the management of colorectal liver metastases by radiation therapy. *Technol Cancer Res Treat*. 2018;17:1533033818816080.
68. Filippi AR, Guerrero F, Badellino S, et al. Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer. *Clin Oncol (R Coll Radiol)*. 2016;28(8):505-512.
69. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2018;4(1):e173501.
70. Katoh N, Onishi H, Uchinami Y, et al. Real-Time Tumor-Tracking Radiotherapy and General Stereotactic Body Radiotherapy for Adrenal Metastasis in Patients With Oligometastasis. *Technol Cancer Res Treat*. 2018;17:1533033818809983.
71. Olson RA, Senan S, Harrow S, et al. Quality of Life Outcomes after Stereotactic Ablative Radiotherapy (SABR) vs. Standard of Care Palliative Treatments: A Secondary Analysis of the SABR-COMET Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2019;105(1 suppl):S72-S73.
72. Davis S, Tappenden P, Cantrell A. A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer. London (UK): National Institute for Health and Care Excellence (NICE); 2012: https://www.ncbi.nlm.nih.gov/books/NBK425826/pdf/Bookshelf_NBK425826.pdf. Accessed 2020 Nov 19.
73. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(2):138-144.
74. Nussbaumer-Streit B, Klerings I, Dobrescu AI, et al. Excluding non-English publications from evidence-syntheses did not change conclusions: a meta-epidemiological study. *J Clin Epidemiol*. 2020;118:42-54.

Appendix 1: Analytical Framework

Figure 1: Analytical Framework



FFP = freedom from progression; LC = lesional control; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SABR = stereotactic ablative radiotherapy.

Appendix 2: Literature Search Methods

Clinical Literature Search

Overview	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	March 20, 2020
Alerts:	Monthly search updates until project completion. After completion search alerts will occur every 3 months.
Study types:	No publication type filters will be applied.
Limits:	Publication date limit: 1990-present Language limit: none Conference abstracts: excluded
Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CCTR)
.dq	Candidate term word (Embase)
.pt	Publication type
.my	Device index terms word (Embase)
.dv	Device trade name (Embase)
.dm	Device manufacturer (Embase)
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multi-Database Strategy	
Line #	Search Strategy
1	(exp radiotherapy/ or radiotherapy.fs.) and (stereo?ta* or stereo ta*).ti,ab,kf,kw.
2	((stereo?ta* or stereo ta*) adj5 (ablat* or body or lung* or liver* or spin*) adj5 (radiat* or radio therap* or radio?therap* or radio surg* or radiosur* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kf,kw.
3	((stereo?ta* or stereo ta* or intensity modul* or linear accelerat*) adj4 (radiat* or radio therap* or radio?therap* or radio surg* or radiosur* or irradiation* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kf,kw.
4	((fraction* or ultra hypofraction* or ultrahypofraction* or hypofraction* or hyperfraction*) adj4 (radio therap* or radio?therap* or radio surg* or radiosur* or irradiation* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kf,kw.
5	((dynamic* or volumetric modul*) adj5 (ARC or wave ARC* or waveARC*).ti,ab,kf,kw.
6	(precision* adj5 deliver* adj5 system*).ti,ab,kf,kw.
7	(fraction* adj5 (stereo ta* or stereota*).ti,ab,kf,kw.
8	(SRS* or SABR* or SBRT* or mdSBRT* or FSR or FSRT or LINAC* or DCA or VMAT or IMRS or IMPT or stereo tatic RT* or stereotatic RT* or stereo taxic RT* or stereotaxic RT* or systemSRBT*).ti,ab,kf,kw.
9	(xknife* or infinity* or novalis* or trilogy* or clinac* or accuray* or radixac* or cyberknife* or cyber knife* or synergy* or gammaknife* or gamma knife* or exactrac* or exac trac* or truebeam* or true beam* or MRLinac* or MR Linac* or eclipse* or rapid ARC* or rapidARC* or prefexion* or vero* or model u*2 or modelu* or modelc* or model c*2).ti,ab,kf,kw.
10	(integra or elekta* or varian or brainlab* or brain lab* or Mitsubishi Heavy*).ti,ab,kf,kw.
11	(versa*3 or precise*3 or edge*3).ti,kf,kw.
12	or/1-11
13	exp Neoplasm Metastasis/ and oligo*.ti,ab,kf,kw.
14	(oligomet* or oligoprogres* or oligorecur* or oligopersis* or oligofraction* or oligoclonal* or oligosynchron*).ti,ab,kf,kw.
15	(oligo* adj5 (meta* or progres* or recur* or persis* or fraction* or clonal* or synchron*).ti,ab,kf,kw.
16	((tumor* or tumour* or cancer* or neoplasm* or carcinoma*) adj3 (migration* or spread*).ti,ab,kf,kw.
17	((few* or limited* or advanced* or number*) adj2 (tumor* or tumour* or site* or metastases or spread or micrometastas*).ti,ab,kf,kw.
18	((transitional or intermediate) adj5 (metasta* or micrometastas*).ti,ab,kf,kw.
19	Limited Metastatic.ti,ab,kf,kw.
20	(secondary adj5 (tumor* or tumour* or lesion* or metastases or micrometastas*).ti,ab,kf,kw.
21	or/13-20
22	12 and 21
23	22 use medall
24	22 use cctr
25	(exp radiosurgery/ or exp radiotherapy equipment/ or exp radiotherapy/ or radiotherapy.fs.) and (stereo?ta* or stereo ta*).ti,ab,kw,dq.
26	((stereo?ta* or stereo ta*) adj5 (ablat* or body or lung* or liver* or spin*) adj5 (radiat* or radio therap* or radio?therap* or radio surg* or radiosur* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kw,dq.
27	((stereo?ta* or stereo ta* or intensity modul* or linear accelerat*) adj4 (radiat* or radio therap* or radio?therap* or radio surg* or radiosur* or irradiation* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kw,dq.
28	((fraction* or ultra hypofraction* or ultrahypofraction* or hypofraction* or hyperfraction*) adj4 (radio therap* or radio?therap* or radio surg* or radiosur* or irradiation* or radio frequen* or radiofrequen* or proton* or photon*).ti,ab,kw,dq.
29	((dynamic* or volumetric modul*) adj5 (ARC or wave ARC* or waveARC*).ti,ab,kw,dq.
30	(precision* adj5 deliver* adj5 system*).ti,ab,kw,dq.
31	(fraction* adj5 (stereo ta* or stereota*).ti,ab,kw,dq.

Multi-Database Strategy	
Line #	Search Strategy
32	(SRS* or SABR* or SBRT* or mdSBRT* or FSR or FSRT or LINAC* or DCA or VMAT or IMRS or IMPT or stereo tatic RT* or stereotatic RT* or stereo tatic RT* or stereotaxic RT* or systemSBRT*).ti,ab,kw,dq.
33	(xknife* or infinity* or novalis* or trilog* or clinac* or accuray* or radixac* or cyberknife* or cyber knife* or synergy* or gammaknife* or gamma knife* or exactrac* or exac trac* or truebeam* or true beam* or MRLinac* or MR Linac* or eclipse* or rapid ARC* or rapidARC* or prefexion* or vero* or model u*2 or modelu*or modelc* or model c*2).ti,ab,kw,dq,my,dv,dm.
34	(integra or elekta* or varian or brainlab* or brain lab* or Mitsubishi Heavy*).ti,ab,kw,dq,dv,dm.
35	(versa*3 or precise*3 or edge*3).ti,kw,dq,my,dv,dm.
36	or/25-35
37	exp metastasis/ and oligo*.ti,ab,kw,dq.
38	(oligomet* or oligoprogres* or oligorecur* or oligopersis* or oligofraction* or oligoclonal* or oligosynchron*).ti,ab,kw,dq.
39	(oligo* adj5 (meta* or progres* or recur* or persis* or fraction* or clonal* or synchron*).ti,ab,kw,dq.
40	((tumor* or tumour* or cancer* or neoplasm* or carcinoma*) adj3 (migration* or spread*).ti,ab,kw,dq.
41	((few* or limited* or advanced* or number*) adj2 (tumor* or tumour* or site* or metastases or spread or micrometastas*).ti,ab,kw,dq.
42	((transitional or intermediate) adj5 (metasta* or micrometastas*).ti,ab,kw,dq.
43	Limited Metastatic.ti,ab,kw,dq.
44	(secondary adj5 (tumor* or tumour* or lesion* or metastases or micrometastas*).ti,ab,kw,dq.
45	or/37-44
46	36 and 45
47	46 use oemezd
48	47 not conference abstract.pt.
49	23 or 24 or 48
50	limit 49 to yr=1990-current
51	remove duplicates from 50

Clinical Trial Registries	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms will include - Stereotactic Ablative Radiotherapy (SABR) OR Stereotactic Radiosurgery (SRS) OR stereotactic body radiation therapy (SBRT) OR fractionated stereotactic radiotherapy (FSRT) OR LINAC OR XKnife OR Versa OR Infinity OR Precise OR Novalis Tx OR Trilogy OR Clinac OR Accuray Tomotherapy OR Radixac OR CyberKnife OR Synergy OR Gamma Knife Icon OR ExacTrac OR TrueBeam OR Edge OR Eclipse RapidArc OR Gamma Knife Model U OR Gamma Knife Model C OR Gamma Knife Prefexion]
Health Canada. Clinical Trials Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms will include - Stereotactic Ablative Radiotherapy (SABR) OR Stereotactic Radiosurgery (SRS) OR stereotactic body radiation therapy (SBRT) OR fractionated stereotactic radiotherapy (FSRT) OR LINAC OR XKnife OR Versa OR Infinity OR Precise OR Novalis Tx OR Trilogy OR Clinac OR Accuray Tomotherapy OR Radixac OR CyberKnife OR Synergy OR Gamma Knife Icon OR ExacTrac OR TrueBeam OR Edge OR Eclipse RapidArc OR Gamma Knife Model U OR Gamma Knife Model C OR Gamma Knife Prefexion]
Canadian Cancer Trials	Produced by the Canadian Partnership Against Cancer Corporation. Targeted search used to capture registered clinical trials. [Search terms will include - Stereotactic Ablative Radiotherapy (SABR) OR Stereotactic Radiosurgery (SRS) OR stereotactic body radiation therapy (SBRT) OR fractionated stereotactic radiotherapy (FSRT) OR LINAC OR XKnife OR Versa OR Infinity OR Precise OR Novalis Tx OR Trilogy OR Clinac OR Accuray Tomotherapy OR Radixac OR CyberKnife OR Synergy OR Gamma Knife Icon OR ExacTrac OR TrueBeam OR Edge OR Eclipse RapidArc OR Gamma Knife Model U OR Gamma Knife Model C OR Gamma Knife Prefexion]

Grey Literature

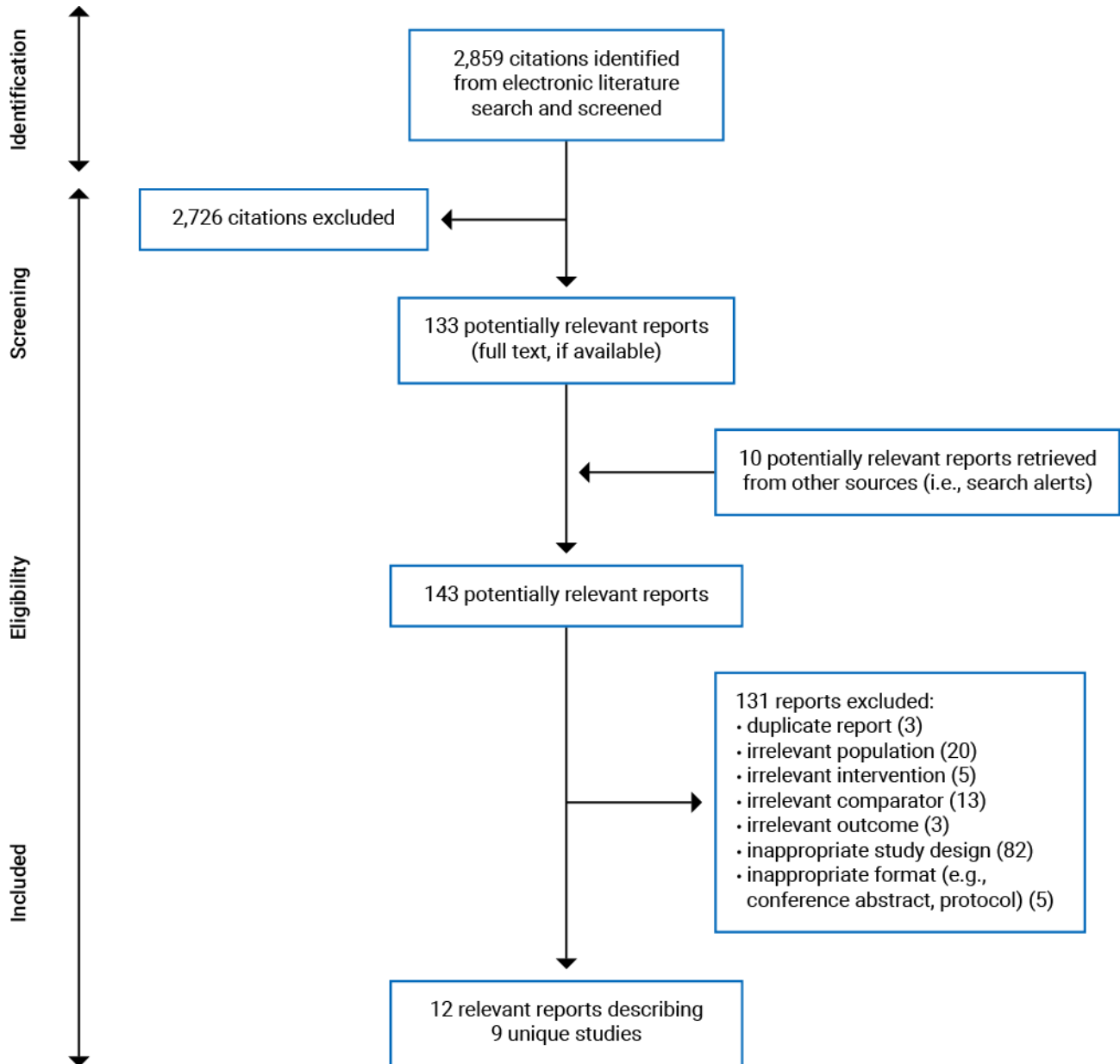
Dates for Search:	April 27, 2020 to May 07, 2020
Keywords:	Stereotactic Ablative Radiotherapy (SABR) OR Stereotactic Radiosurgery (SRS) OR stereotactic body radiation therapy (SBRT) OR fractionated stereotactic radiotherapy (FSRT) OR LINAC OR XKnife OR Versa OR Infinity OR Precise OR Novalis Tx OR Trilogy OR Clinac OR Accuray Tomotherapy OR Radixac OR CyberKnife OR Synergy OR Gamma Knife Icon OR ExacTrac OR TrueBeam OR Edge OR Eclipse RapidArc OR Gamma Knife Model U OR Gamma Knife Model C OR Gamma Knife Prefexion
Limits:	Publication years: 1990-present

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool For Searching Health-Related Grey Literature (<https://www.cadth.ca/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 3: PRISMA Flow Chart of Selected Reports

Figure 2: PRISMA Flow Chart of Selected Reports



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Appendix 4: List of Included Studies

1. Hurmuz P, Onal C, Ozyigit G, et al. Treatment outcomes of metastasis-directed treatment using (68)Ga-PSMA-PET/CT for oligometastatic or oligorecurrent prostate cancer: Turkish Society for Radiation Oncology group study (TROD 09-002). *Strahlenther Onkol.* 2020;196(11):1034-1043.
2. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol.* 2020;38(25):2830-2838.
3. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(5):650-659.
4. van de Ven S, van den Bongard D, Pielkenrood B, et al. Patient-Reported Outcomes of Oligometastatic Patients After Conventional or Stereotactic Radiation Therapy to Bone Metastases: An Analysis of the PRESENT Cohort. *Int J Radiat Oncol Biol Phys.* 2020;107(1):39-47.
5. De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol.* 2019;76(6):732-739.
6. Olson R, Senan S, Harrow S, et al. Quality of Life Outcomes After Stereotactic Ablative Radiation Therapy (SABR) Versus Standard of Care Treatments in the Oligometastatic Setting: A Secondary Analysis of the SABR-COMET Randomized Trial. *Int J Radiat Oncol Biol Phys.* 2019;105(5):943-947.
7. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet.* 2019;393(10185):2051-2058.
8. He Z, Chen G, Ouyang B, et al. Conformal radiation therapy or stereotactic body radiation therapy: Institutional experience in the management of colorectal liver metastases by radiation therapy. *Technol Cancer Res Treat.* 2018;17.
9. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2018;4(1):e173501.
10. Lodeweges JE, Klinkenberg TJ, Ubbels JF, Groen HJM, Langendijk JA, Widder J. Long-term Outcome of Surgery or Stereotactic Radiotherapy for Lung Oligometastases. *J Thorac Oncol.* 2017;12(9):1442-1445.
11. Filippi AR, Guerrero F, Badellino S, et al. Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer. *Clin Oncol (R Coll Radiol).* 2016;28(8):505-512.
12. Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? *Radiother Oncol.* 2013;107(3):409-413.

Appendix 5: List of Excluded Studies and Reasons for Exclusion

Duplicate Report (n = 3)

1. McDonald F, Hanna GG. Oligoprogressive Oncogene-addicted Lung Tumours: Does Stereotactic Body Radiotherapy Have a Role? Introducing the HALT Trial. *Clin Oncol (R Coll Radiol)*. 2018;30(1):1-4.
2. Trovo M, Furlan C, Polesel J, et al. Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial. *Radiother Oncol*. 2018;126(1):177-180.
3. Kao J, Timmins J, Ozao-Choy J, Packer S. Effects of combined sunitinib and extracranial stereotactic radiotherapy on bone marrow hematopoiesis. *Oncol Lett*. 2016;12(3):2139-2144.

Irrelevant Population (n = 20)

1. Deek MP, Taparra K, Phillips R, et al. Metastasis-directed Therapy Prolongs Efficacy of Systemic Therapy and Improves Clinical Outcomes in Oligoprogressive Castration-resistant Prostate Cancer. *Eur Urol Oncol*. 2020.
2. Papadopoulos KP, Johnson ML, Lockhart AC, et al. First-In-Human Study of Cemiplimab Alone or In Combination with Radiotherapy and/or Low-dose Cyclophosphamide in Patients with Advanced Malignancies. *Clin Cancer Res*. 2020;26(5):1025-1033.
3. Schullian P, Putzer D, Laimer G, Levy E, Bale R. Feasibility, safety, and long-term efficacy of stereotactic radiofrequency ablation for tumors adjacent to the diaphragm in the hepatic dome: a case-control study. *Eur Radiol*. 2020;30(2):950-960.
4. Schullian P, Putzer D, Silva MA, Laimer G, Kolbitsch C, Bale R. Stereotactic Radiofrequency Ablation of Liver Tumors in Octogenarians. *Front Oncol*. 2019;9:929.
5. Shen PC, Chang WC, Lo CH, et al. Comparison of Stereotactic Body Radiation Therapy and Transarterial Chemoembolization for Unresectable Medium-Sized Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys*. 2019;105(2):307-318.
6. Franzese C, Comito T, Clerici E, et al. Liver metastases from colorectal cancer: propensity score-based comparison of stereotactic body radiation therapy vs. microwave ablation. *J Cancer Res Clin Oncol*. 2018;144(9):1777-1783.
7. Ost P, Reynders D, Decaestecker K, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2018;36(5):446-453.
8. Sapir E, Tao Y, Schipper MJ, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100(1):122-130.
9. Schulz D, Wirth M, Piontek G, et al. Improved overall survival in head and neck cancer patients after specific therapy of distant metastases. *Eur Arch Otorhinolaryngol*. 2018;275(5):1239-1247.
10. Sprave T, Verma V, Forster R, et al. Quality of Life Following Stereotactic Body Radiotherapy Versus Three-Dimensional Conformal Radiotherapy for Vertebral Metastases: Secondary Analysis of an Exploratory Phase II Randomized Trial. *Anticancer Res*. 2018;38(8):4961-4968.
11. Stenman M, Sinclair G, Paavola P, Wersall P, Harmenberg U, Lindskog M. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at 2 Swedish centres 2005-2014. *Radiother Oncol*. 2018;127(3):501-506.
12. Fleming C, Rimner A, Foster A, Woo KM, Zhang Z, Wu AJ. Palliative efficacy and local control of conventional radiotherapy for lung metastases. *Ann*. 2017;6(Suppl 1):S21-S27.
13. Moon SH, Cho KH, Lee CG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: Survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). *Strahlenther Onkol*. 2016;192(6):377-385.
14. Reijneveld JC, Taphoorn MJB, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. 2016;17(11):1533-1542.

15. Jacob R, Turley F, Redden DT, et al. Adjuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non-resectable hepatocellular carcinoma tumours of ≥ 3 cm. *HPB (Oxford)*. 2015;17(2):140-149.
16. Langendijk H, Kaanders JH, Doornaert P, et al. POPART vs CPORT in squamous cell head and neck cancer: Results of a multicenter randomised study of the Dutch head and neck Study Group. *Radiother Oncol*. 2015;114:9-10.
17. Jiang Z, Wang Q, Yang G, et al. Optimized treatment with RF thermotherapy and immunotherapy combined with CyberKnife for advanced high-risk tumors: A clinical trial report. *Biomed Rep*. 2014;2(2):245-249.
18. Yu W, Tang L, Lin F, et al. Stereotactic radiosurgery, a potential alternative treatment for pulmonary metastases from osteosarcoma. *Int J Oncol*. 2014;44(4):1091-1098.
19. Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer*. 2008;8:351.
20. Guo J, Sun XN, Huang M. Evaluation of the efficacy for alternated treatment on primary liver cancer by interventional therapy in combination with fractionated stereotactic conformal radiotherapy. *Chin J Clin Oncol*. 2005;32(24):1418-1420.

Irrelevant Intervention (n = 5)

1. Chan OSH, Lam KC, Li JYC, et al. ATOM: A phase II study to assess efficacy of preemptive local ablative therapy to residual oligometastases of NSCLC after EGFR TKI. *Lung Cancer*. 2020;142:41-46.
2. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol*. 2019;37(18):1558-1565.
3. Steuber T, Jilg C, Tennstedt P, et al. Standard of Care Versus Metastases-directed Therapy for PET-detected Nodal Oligorecurrent Prostate Cancer Following Multimodality Treatment: A Multi-institutional Case-control Study. *Eur Urol Focus*. 2019;5(6):1007-1013.
4. Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW. The Role of Radiotherapy in Epidermal Growth Factor Receptor Mutation-positive Patients with Oligoprogression: A Matched-cohort Analysis. *Clin Oncol (R Coll Radiol)*. 2017;29(9):568-575.
5. Roos DE, Turner SL, O'Brien PC, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol*. 2005;75(1):54-63.

Irrelevant Comparator (n = 13)

1. Franzese C, Comito T, Vigano L, et al. Liver Metastases-directed Therapy in the Management of Oligometastatic Breast Cancer. *Clin Breast Cancer*. 2020;20(6):480-486.
2. Kalinauskaite GG, Tinhofer, II, Kufeld MM, et al. Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. *BMC Cancer*. 2020;20(1):404.
3. Desideri I, Francolini G, Scotti V, et al. Benefit of ablative versus palliative-only radiotherapy in combination with nivolumab in patients affected by metastatic kidney and lung cancer. *Clin Transl Oncol*. 2019;21(7):933-938.
4. Lepinoy A, Silva YE, Martin E, et al. Salvage extended field or involved field nodal irradiation in (18)F-fluorocholine PET/CT oligorecurrent nodal failures from prostate cancer. *Eur J Nucl Med Mol Imaging*. 2019;46(1):40-48.
5. Fanetti G, Marvaso G, Ciardo D, et al. Stereotactic body radiotherapy for castration-sensitive prostate cancer bone oligometastases. *Med Oncol*. 2018;35(5):75.
6. Frost N, Tessmer A, Schmittel A, et al. Local ablative treatment for synchronous single organ oligometastatic lung cancer-A propensity score analysis of 180 patients. *Lung Cancer*. 2018;125:164-173.
7. Kato H, Onishi H, Uchinami Y, et al. Real-Time Tumor-Tracking Radiotherapy and General Stereotactic Body Radiotherapy for Adrenal Metastasis in Patients with Oligometastasis. *Technol Cancer Res Treat*. 2018;17:1533033818809983.

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Inappropriate Format (For Example, Conference Abstract, Protocol; n = 5):

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Appendix 6: Considerations for Meta-Analyses

Table 16: Rationale for Not Conducting Meta-Analysis

Outcome	Intervention	Comparator	Relevant studies	Meta-analysis appropriate?
Question 1: Clinical Effectiveness				
OS	SABR plus SOC ^a	SOC	RCTs: SABR-COMET: Palma et al. (2019) ³² and Palma et al. (2020) ⁵⁸ Iyengar et al. (2018) ⁶⁹	No: Data unavailability (i.e., HRs available for 1 of 2 studies)
	SABR	SOC	NRSs: Hurmuz et al. (2020) ⁶⁵ van de Ven et al. (2020) ⁶⁴ He et al. (2018) ⁶⁷ Filippi et al. (2016) ⁶⁸ Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ⁶¹	No: Discordant results (i.e., large variability in the direction, magnitude, and statistical significance of the results)
PFS	SABR plus SOC	SOC	RCTs: SABR-COMET: Palma et al. (2019) ³² and Palma et al. (2020) ⁵⁸ Iyengar et al. (2018) ⁶⁹	No: No statistical gain (i.e., point estimates similar in direction, magnitude, and statistical significance leading to no added value in pooling)
	SABR	SOC	RCT: Phillips et al. (2020) ⁶³ NRSs: Hurmuz et al. (2020) ⁶⁵ van de Ven et al. (2020) ⁶⁴ Filippi et al. (2016) ⁶⁸ Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ⁶¹	No: One study No: Data unavailability (i.e., HRs available for 2 studies)
Question 2: Safety				
AEs	SABR plus SOC	SOC	RCTs: SABR-COMET: Palma et al. (2019) ³² and Palma et al. (2020) ⁵⁸ Iyengar et al. (2018) ⁶⁹	No: Data variability (e.g., AEs included different AE grades reported, treatment versus non-treatment-related AEs, or event data versus patient data)
	SABR	SOC	RCT: Phillips et al. (2020) ⁶³ NRSs: De Bleser et al. (2019) ⁶⁶ He et al. (2018) ⁶⁷ Filippi et al. (2016) ⁶⁸	No: One study No: Data variability (e.g., AEs included different AE grades reported, treatment versus non-treatment-related AEs, or event data versus patient data)

AE = adverse event; HR = hazard ratio; NRS = nonrandomized study; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SOC = standard of care.

^a SOC may include surgery, conventional radiotherapy, chemotherapy, immunotherapy, hormonotherapy, other ablative treatment, targeted therapy, or no treatment (observation).

Appendix 7: Characteristics of Included Publications

Table 17: Characteristics of Included Primary Studies

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
RCTs					
<p>Phillips et al., 2020⁶³ US Trial acronym: ORIOLE (NCT02680587) Funding source: Nesbitt-McMaster Foundation, Ronald Rose and Joan Lazar, Movember Foundation, Prostate Cancer Foundation, and the NCI; SDW/DT and Shanahan Cancer Research Funds; NIH Director’s New Innovator Award; Virginia and D.K. Ludwig Fund for Cancer Research; CRK Faculty Scholar Fund; Transdisciplinary Integration of Population Science Program of Sidney Kimmel Cancer Center–Jefferson Health, and a Challenge Grant from the Prostate Cancer Foundation.</p>	<p>RCT, phase II, open-label, parallel trial from 3 US radiation treatment facilities affiliated within a university hospital. Two-sided Fisher exact test used for comparisons of progression events. The Kaplan-Meier method used to calculate PFS and the P values were calculated using the log-rank test. The Holm-Šidák method for multiple t tests was used to compare Brief Pain Inventory responses (QoL outcome) between and within arms across time. All analysis was performed on an ITT basis. Median follow-up (IQR): Total: 18.8 (5.8 to 35.0) months.</p>	<p>Inclusion criteria: Adult patients (≥ 18 years of age) with recurrent hormone-sensitive prostate cancer and 1 to 3 asymptomatic metastatic tumours of the bone or soft tissue within the prior 6 months that are ≥ 5.0 cm on the largest axis or 250 cm². Certain hematology values must have been within a certain range to qualify (PSA, testosterone, leukocytes, neutrophils). Primary tumours were treated with surgery or radiation or both. ADT was not allowed within 6 months of enrolment. Patients must have a life expectancy ≥ 12 months and an ECOG performance status ≤ 2. Locations of metastasis were bone or soft tissue.</p>	<p>Total N = 54 Median age (IQR): • SABR: 68 (61 to 70) years • observation: 68 (64 to 76) years Sex, % male: 100.0 Number of metastases per patient: 1 to 3 • Mean (nodal) = 1.39 (SABR), 1.22 (observation) • Mean (bone) = 0.64 (SABR), 0.44 (observation)</p>	<p>SABR (n = 36) • Dose: 19.5 to 48.0 Gy in 3 to 5 fractions • Equipment: NR Observation (n = 18) • Details NR</p>	<p>Research questions: 1, 2 Outcomes Primary: • progression events Secondary: • PFS • AEs • QoL Definitions: • Progression = a PSA rise ≥ 2 ng/dL and 25% above nadir; concern for radiologic progression by CT, MRI, or bone scan as determined by the reading radiologist; initiation of ADT; or death. Withdrawal from the study after randomization was considered progression. • PFS = Time from starting of treatment to time of progression.</p>

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
		Exclusion criteria: Patients who previously received more than 3 years of ADT, received ADT in the prior 6 months, or developed castration-resistant disease; patients with spinal cord compression, suspected pulmonary or liver metastases > 10 mm in largest axis, and received other investigational drugs; patients with certain hematology values outside a specific range (serum creatinine, bilirubin, transaminases).			<ul style="list-style-type: none"> • AEs: Assessed by CTCAE version 4.0 • QoL: Assessed using Brief Pain Inventory (Short Form)
SABR-COMET Palma et al. (2019), ³² Palma et al. (2020), ⁵⁸ and Olson et al. (2019) ⁵⁹ Canada, the Netherlands, UK, and Australia Trial acronym: SABR-COMET (NCT01446744) Funding source: Ontario Institute for Cancer Research and a London Regional Cancer Program Catalyst Grant.	RCT, phase II, open-label, parallel trial from 10 hospital centres. A chi-square test or Fisher exact test was used to compare differences in rates of grade 2 or higher toxicity and LC rate between groups. The Kaplan-Meier method were used to calculate OS and PFS, and the stratified log-rank test was used to compared differences. Hazard ratios were calculated using Cox regression adjusted for	Inclusion criteria: Adult patients (≥ 18 years of age) with 1 to 5 metastases in total and a maximum of 3 metastases in any single organ system (e.g., lung, liver, brain, bone), with good ECOG performance status (score 0 to 1), and a life expectancy of at least 6 months. The primary tumour had to have been treated definitively by resection, radiofrequency ablation, or radiotherapy at least 3 months before	Total N = 99 Median age (IQR): <ul style="list-style-type: none"> • SABR + systemic therapy: 66.8 (42.8 to 89.4) years • systemic therapy: 68.6 (44.2 to 87.0) years Sex, % male: <ul style="list-style-type: none"> • SABR + systemic therapy: 61 • systemic therapy: 58^{58,59} Gender, % men: ^a <ul style="list-style-type: none"> • SABR + systemic therapy: 61 • systemic therapy: 58³² 	SABR + Systemic therapy (n = 66) <ul style="list-style-type: none"> • Systemic therapy = choice of systemic drugs at the discretion of the medical oncologist • SABR dose: 30 Gy to 60 Gy in 3 to 8 fractions depending on target size and location. Single fractions of 16 Gy to 24 Gy were permitted for target in brain and vertebrae • SABR equipment: Not specified; treatment 	Research questions: 1, ^{32,58,59} ² ^{32,58} Outcomes Primary: <ul style="list-style-type: none"> • OS^{32,58} Secondary: <ul style="list-style-type: none"> • PFS^{32,58} • toxicity^{32,58} • proportion of patients with LC^{32,58} • QoL^{32,58,59} Definitions:

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
	<p>stratification. All analysis was performed on an ITT basis.</p> <p>Short-term follow-up Median follow-up (IQR): SABR + systemic therapy: 26 (23 to 37) months Systemic therapy: 25 (19 to 54) months³²</p> <p>Long-term follow-up Median follow-up (IQR): Total: 51 (46 to 58) month⁵⁵⁸</p>	<p>enrolment with no progression at that site since definitive treatment. Locations of primary tumour were breast, colorectal, lung, prostate, and other. Location of metastases included adrenal, bone, liver, lung, and other (brain [3 lesions in systemic therapy; 1 lesion in SABR + systemic therapy], lymph nodes [1 lesion in control, 3 lesions in SABR + systemic therapy], and para-renal [1 in systemic therapy]). Metastases had to have been previously treated and controlled by resection, radiofrequency ablation, or radiotherapy.</p> <p>Exclusion criteria: Patients with serious comorbidities that preclude radiotherapy, metastasis in a femoral bone, hormone-sensitive disease, 1 to 3 brain metastases and no disease elsewhere, prior radiotherapy to a site requiring treatment, malignant pleural effusion, clinical or radiologic evidence of spinal cord compression OR tumour</p>	<p>Number of metastases per patient:</p> <ul style="list-style-type: none"> • 1 to 5; mean NR 	<ul style="list-style-type: none"> • delivery with static beams (either 3DCRT or intensity-modulated) or rotational therapy (VMAT or tomotherapy) <p>Systemic therapy (n = 33)</p> <ul style="list-style-type: none"> • Systemic therapy = choice of systemic drugs at the discretion of the medical oncologist • Radiotherapy was also delivered according to the principles of palliative radiotherapy as per the individual institution, with the goal of alleviating symptoms or preventing imminent complications • Depending on tumour location and indication, treatment dose ranged from 8 Gy in 1 fraction to 30 Gy in 10 fractions. 	<ul style="list-style-type: none"> • OS = Time from randomization to death from any cause • PFS = Time from randomization to disease progression at any site or death • LC = The absence of progression in the lesions initially present at randomization • Toxicity = Assessed by CTCAE version 4.0 • QoL = Assessed using FACT-G

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
		within 3 mm of spinal cord on MRI, dominant brain metastasis requiring surgical decompression, pregnancy, or lactation.			
Iyengar et al. (2018)⁶⁹ US Trial acronym: NR (NCT02045446) Funding source: NR	RCT, phase II, open-label, parallel trial from a single institution. Survival analyses for PFS and OS were performed using Kaplan-Meier method. The log-rank test was used to test for difference between groups. All analysis was performed on an ITT basis. Median follow-up (IQR): Total: 9.6 (2.4 to 30.2) months	Inclusion criteria: Adult patients (≥ 18 years of age) with a Karnofsky Performance Scale score of 70+, with biopsy-proven metastatic lung (NSCLC; stage IV). Metastases allowed per patient were 1 to 5 lesions with no more than 3 sites in the liver or lung. Primary tumour (lung) had been treated with platinum-based chemotherapy, achieving stable disease or a partial response on imaging by RECIST. Locations of metastasis were lung, adrenal, mediastinum, axilla, liver, nasopharynx, bone (rib, spine). Exclusion criteria: Patients receiving first-line targeted therapy for EGFR-positive or ALK-positive lung (NSCLC); patients with previously irradiated primary disease progressed within 3 months of that	Total N = 29 Median age (IQR): SABR + maintenance chemotherapy: 63.5 (51.0; 78.0) years Maintenance chemotherapy: 70.0 (51.0; 79.0) years Sex; % male SABR + maintenance chemotherapy: 64.3 Maintenance chemotherapy: 73.3 Number of metastases per patient: NR; mean NR	SABR + maintenance chemotherapy (n = 14) SABR dose: 21 to 27 Gy in 1 fraction; 26.5 to 33 Gy in 3 fractions; 30 to 37.5 Gy in 5 fractions SABR equipment: Conventional linear accelerators and specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) were allowed as well as specialized accelerators (CyberKnife or tomotherapy) maintenance chemotherapy = erlotinib, pemetrexed, docetaxel, gemcitabine, or bevacizumab Maintenance chemotherapy (n = 15) erlotinib, pemetrexed, docetaxel, gemcitabine, or bevacizumab	Research Questions: 1, 2 Outcomes Primary: PFS Secondary: OS progression events toxicity Definitions: OS = Time to death from any cause PFS = Time to development of new lesions, progression of existing lesions, or death, which ever came first Toxicity = Assessed by CTCAE version 4.0

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
		treatment; patients with untreated or uncontrolled brain metastases or disease involving the gastrointestinal tract and skin.			
NRSs					
Hurmuz et al. (2020) ⁶⁵ Turkey Trial acronym: TROG Funding source: NR	Retrospective cohort study from 10 institutions. The Kaplan-Meier method was used to calculate OS and PFS rates. Univariate analysis was performed via the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model, using covariates with a P value of less than 0.05 in univariate analysis. Median follow-up (IQR): • Total: 22.9 (3.3 to 77.8) months	Inclusion criteria: Patients with biopsy-proven prostate cancer (treated between 2014 and 2019) and synchronous or metachronous bone or lymph node metastasis limited to ≤ 5 sites detected with 68Ga-PSMA-PET/CT and with a minimum of 3 months of follow-up after MDT. Patients included hormone-naïve, hormone-sensitive, or castration-resistant disease; concurrent ADT or chemotherapy at the time of SBRT was allowed. Exclusion criteria: Patients with ECOG performance status of ≥ 2 and patients treated previously with radiotherapy to the same oligometastatic site.	Total N = 176 Median age (range): • Total: 65 (42 to 84) years Sex, % male: 100.0 Number of metastases per patient: • NR; mean NR	SABR with or without hormonotherapy (n = 129) • Median fraction number: 3 (range 1 to 5) • Median fraction dose: 9 Gy (range 5 Gy to 24 Gy) • Total SABR doses: 27 Gy (range 15 Gy to 40 Gy) • SABR equipment: NR Conventional RT with or without hormonotherapy (n = 47) • Median fraction number: 28 (range of 25 to 39) • Median fraction dose: 2 Gy (range 1.8 Gy to 2.0 Gy) • Total radiation doses: 60 Gy (range 40 Gy to 78 Gy)	Research question: 1 Outcomes • OS • PFS • Local progression events Definitions: • OS = Definition NR • PFS = Definition NR

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
<p>van de Ven et al. (2020)⁶⁴</p> <p>The Netherlands</p> <p>Trial acronym: PRESENT (NCT02356497)</p> <p>Funding source: NR</p>	<p>Prospective cohort study (subset of patients with oligometastatic disease from full PRESENT cohort) from single institution.</p> <p>Linear mixed models for repeated measures were used to compared QoL between groups. All QoL analyses were adjusted for primary tumour, WHO performance status, presence of non-bone metastases, number of metastases, whether all metastases were treated at baseline, and pain at baseline. Survival outcomes were assessed using the Kaplan-Meier method and were compared using the log-rank test.</p> <p>Median follow-up (IQR):</p> <ul style="list-style-type: none"> • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months 	<p>Inclusion criteria:</p> <p>Adult patients (≥ 18 years of age) with either synchronous or metachronous oligometastatic disease (≤ 5 metastatic lesions within ≤ 3 different organs). Primary tumours were located at various sites (prostate, breast, lung [NSCLC], kidney, other). Some patients had received treatment of primary tumour and previous treatment of metastases. Locations of metastasis were bone and other.</p> <p>Exclusion criteria:</p> <p>NR</p>	<p>Total N = 131</p> <p>Mean age:</p> <ul style="list-style-type: none"> • SABR: 64.4 years • 3DCRT: 68.3 years <p>Sex, % male:</p> <ul style="list-style-type: none"> • SABR: 51.4 • 3DCRT: 48.6 <p>Number of metastases per patient:</p> <ul style="list-style-type: none"> • NR; mean NR 	<p>SABR (n = 65)</p> <ul style="list-style-type: none"> • Dose: 18 Gy in 1 fraction (35%); 10 Gy in 3 fractions (30%); 7 Gy in 5 fractions (20%) • Equipment: NR <p>3DCRT (n = 66)</p> <ul style="list-style-type: none"> • Dose: 8 Gy in 1 fraction (44%); 3 Gy in 10 fractions (36%); 4 Gy in 5 fractions (12%) 	<p>Research Question: 1</p> <p>Outcomes</p> <ul style="list-style-type: none"> • OS • PFS • Pain response • QoL <p>Definitions:</p> <ul style="list-style-type: none"> • OS = Definition NR. • PFS = Time from start of radiation therapy until the date of a radiologic confirmed progression event (local or distant), death, or end of follow-up. • Pain response = Defined according to international consensus criteria using NRS and Brief Pain Inventory scores, pain medication and daily oral morphine equivalent based on returned QoL questionnaires or during follow-ups. • QoL = Assessed using global, functional, and role scales): EORTC QLQ-BM22, EORTC QLQ-C15-PAL, Brief Pain Inventory, EQ-5D.

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
<p>De Bleser et al. (2019)⁶⁶ Belgium, Italy, France, Switzerland, UK, Spain Trial acronym: NA Funding source: NIHR</p>	<p>Retrospective cohort study from 15 centres in several European countries. The Fisher exact test was used for comparisons between treatment groups. Median follow-up (IQR):</p> <ul style="list-style-type: none"> Total: 36 (23 to 56) months 	<p>Inclusion criteria: Male adult patients (≥ 18 years of age) with hormone-sensitive nodal metachronous oligorecurrent prostate cancer (5 or fewer lymph nodes). Primary tumours were treated with local therapy (either radical prostatectomy, radiotherapy, or both). Some patients had previous treatment of metastases with ADT (39% in SBRT; 32% in ENRT). Locations of metastasis were pelvic lymph nodes, extra-pelvic lymph nodes, both (i.e., both regional [N1] and distant [M1a] included).</p> <p>Exclusion criteria: Patients with synchronous prostate relapse and bone or visceral metastasis at recurrence; patients having a testosterone level of < 50 ng/dL at the time of metastatic recurrence; patients with oligometastases at primary diagnosis.</p>	<p>Total N = 506 Median age (IQR):</p> <ul style="list-style-type: none"> SABR: 63 (58 to 68) years ENRT: 63 (59 to 68) years <p>Sex, % male: 100.0 Number of metastases per patient:</p> <ul style="list-style-type: none"> NR; mean NR 	<p>SABR with or without ADT (n = 309)</p> <ul style="list-style-type: none"> SABR dose: minimum 5 Gy per fraction, maximum 10 fractions SABR equipment: NR ADT was provided at the discretion of the physician <p>ENRT with or without ADT (n = 197)</p> <ul style="list-style-type: none"> ENRT dose: minimum dose of 45 Gy in 25 fractions (or biological equivalent), with or without a simultaneous integrated boost to the suspicious nodes ADT was provided at the discretion of the physician 	<p>Research Questions: 1, 2 Outcomes</p> <ul style="list-style-type: none"> Local progression events Toxicity <p>Definition:</p> <ul style="list-style-type: none"> Toxicity = Assessed by CTCAE or RTOG grading system

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
<p>He et al. (2018)⁶⁷</p> <p>China</p> <p>Trial acronym: NA</p> <p>Funding source: None</p>	<p>Retrospective cohort study from a single institution.</p> <p>Chi-squared test was used for comparisons between groups. Survival analyses for OS and LCS were performed using the Kaplan-Meier method for univariate analysis and Cox regression model for multivariate analysis.</p> <p>Median follow-up:</p> <ul style="list-style-type: none"> Total: 13 months 	<p>Inclusion criteria:</p> <p>Adult patients (≥ 18 years of age) with colorectal cancer that had been treated with tumour radical resection, post-operative staging IIIA-C (N positive), normal liver function (Child-Pugh class A), and unsuitable for or unwilling to undergo surgical resection.</p> <p>Patients diagnosed with a limited number of metachronous liver metastases (≤ 3 metastatic lesions in the liver per patient).</p> <p>Exclusion criteria:</p> <p>Patients with tumour site exceeding 6 cm in diameter, more than 3 metastatic lesions in the liver, presence or metastatic sites other than liver, and tumour recurrence in the abdomen or pelvis.</p>	<p>Total N = 26</p> <p>Median age (IQR):</p> <ul style="list-style-type: none"> Total: 71 (45 to 87) years <p>Sex, % male:</p> <ul style="list-style-type: none"> SABR: 45.5 3DCRT: 73.3 <p>Number of metastases per patient:</p> <ul style="list-style-type: none"> 1 to 3; mean NR 	<p>SABR (n = 11)</p> <ul style="list-style-type: none"> Dose: 50 Gy in 10 fractions (5 Gy per fraction; 18 lesions) Equipment: Not specified; treatment delivered using 6-MV X-ray from 3 to 5 fields <p>3DCRT (n = 15)</p> <ul style="list-style-type: none"> Dose: 50 Gy in 25 fractions (2 Gy per fraction; 32 lesions) 	<p>Research questions: 1, 2</p> <p>Outcomes</p> <ul style="list-style-type: none"> OS Toxicity <p>Definitions:</p> <ul style="list-style-type: none"> OS = Time from the beginning of radiation therapy to death (or last known living contact) Toxicity = Assessed by CTCAE version 3.0

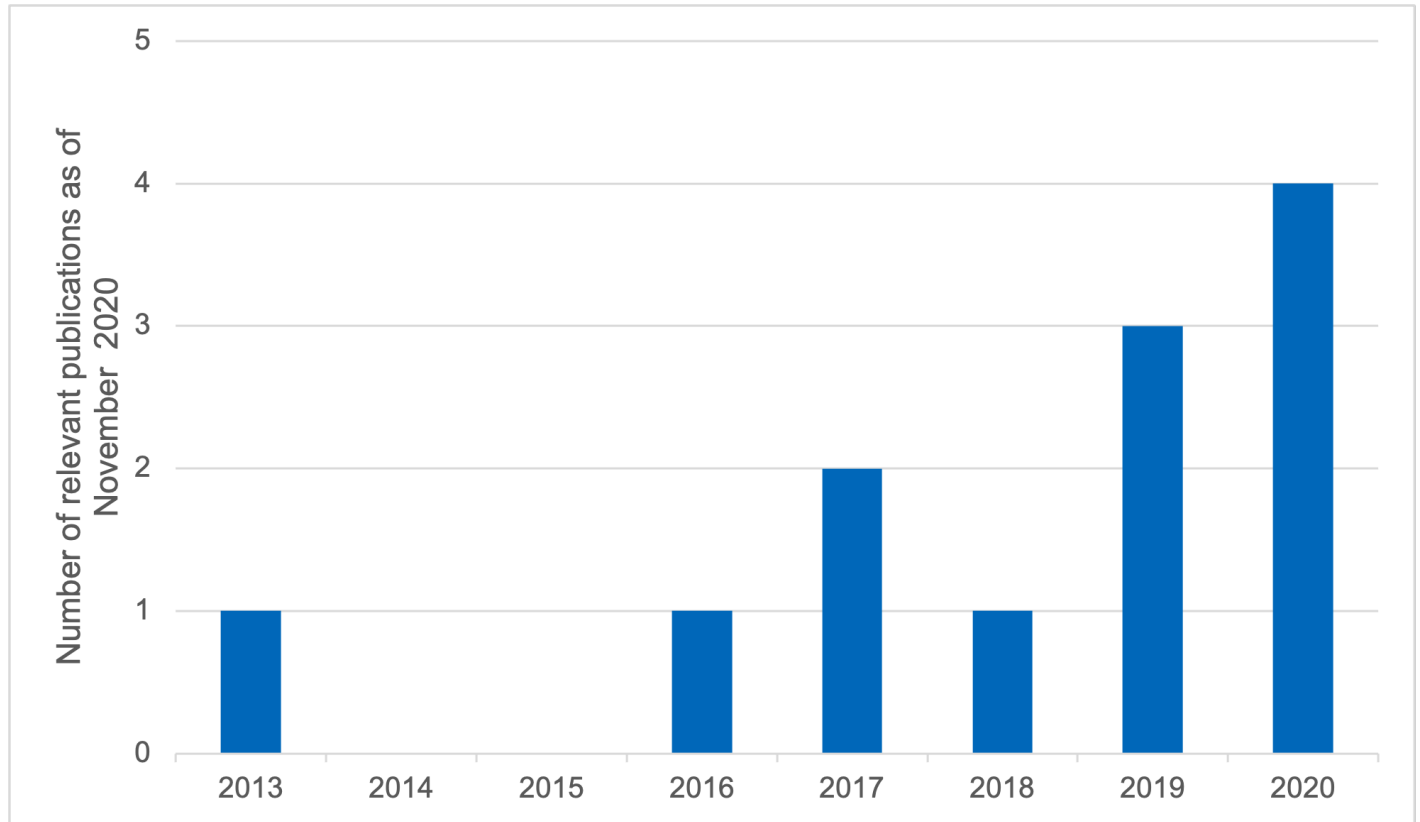
First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
<p>Filippi et al. (2016)⁶⁸</p> <p>Italy</p> <p>Trial acronym: NA</p> <p>Funding source: NR</p>	<p>Retrospective cohort study from a single institution.</p> <p>Chi-square test, Fisher exact test, t test, or Wilcoxon rank sum test were used to compared variables. The Kaplan-Meier method was used to calculate OS and PFS, which were compared using the log-rank test.</p> <p>Median follow-up (IQR):</p> <ul style="list-style-type: none"> • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months 	<p>Inclusion criteria:</p> <p>Adult patients (≥ 18 years of age) with colorectal adenocarcinoma previously treated with radical surgery, both synchronous and metachronous lung metastases (1 to 5 lesions), controlled primary tumour or controlled extra-lung metastases by local therapies or previous systemic therapies. The maximum tumour diameter had to be ≤ 50 mm. Patients must have had adequate pulmonary function and an ECOG performance status of 0 to 1.</p> <p>Exclusion criteria:</p> <p>NR</p>	<p>Total N = 170</p> <p>Median age (IQR):</p> <ul style="list-style-type: none"> • SABR: 72.1 (66.1 to 77.0) years • Surgery: 66.4 (59.3 to 72.4) years <p>Sex; % male:</p> <ul style="list-style-type: none"> • SABR: 50.0 • Surgery: 61.3 <p>Number of metastases per patient:</p> <ul style="list-style-type: none"> • 1 to 5; mean NR 	<p>SABR (n = 28)</p> <ul style="list-style-type: none"> • Doses: 26 Gy in 1 fraction (31 lesions), 45 Gy in 3 fractions (8 lesions), 55 Gy in 10 fractions (2 lesions), and 60 Gy in 8 fractions (2 lesions) • Equipment: Linear accelerator (Elekta Precise, Elekta, Stockholm, Sweden) or IG-VMAT with SABR being delivered with a linear accelerator (Elekta Axesse, Elekta, Stockholm, Sweden). <p>Surgery (n = 142)</p> <ul style="list-style-type: none"> • 5 (3.5%) received a thoroscopic resection, 96 (67.6%) a wedge resection, 37 (26%) an anatomical resection (n = 24 for lobectomy, n = 12 for segmentectomy, n = 1 for pneumonectomy); n = 4 (2.9%) for a combined resection (anatomical resection + wedge resection) 	<p>Research questions: 1, 2</p> <p>Outcomes</p> <ul style="list-style-type: none"> • OS • PFS • Toxicity • All progression events • Local progression events <p>Definitions:</p> <ul style="list-style-type: none"> • OS = Time from the date of treatment for lung metastases (SBRT or surgery) to the date of death from any cause or to the last follow-up • PFS = Time from the date of the treatment for lung metastases (SBRT or surgery) to the date of progression (death or first local or distant recurrence) or to the last follow-up • Toxicity = Assessed by CTCAE version 3.0

First author (publication year) Country Trial acronym (registry ID) Source of funding	Study design, analytical approach, follow-up	Eligibility criteria	Sample size, patient characteristics (age, sex, number of metastases per patient)	Intervention, comparator	Relevant for clinical research question(s) Relevant outcomes measured
Widder et al. (2013)⁶⁰ and Lodeweges et al. (2017)⁶¹ The Netherlands Trial acronym: NA Funding source: NR	Retrospective cohort study from a single institution. Survival times were estimated using the Kaplan-Meier method and differences were assessed using the log-rank test. Short-term follow-up Median follow-up (IQR): <ul style="list-style-type: none"> Total: 43 (36 to 60) months⁶⁰ Long-term follow-up Median follow-up (IQR): <ul style="list-style-type: none"> Total: 91.2 (69.6 to 117.6) month⁶¹ 	Inclusion criteria: Adult patients (≥ 18 years of age) with up to 5 pulmonary metastases from various types of primary tumour (colorectal, sarcoma, lung (NSCLC), kidney, other) previously treated by surgery or thermal ablation. Exclusion criteria: NR	Total N = 110 Median age (IQR): <ul style="list-style-type: none"> SABR: 70 (49 to 89) years Surgery: 61 (18 to 81) years Sex; % male: <ul style="list-style-type: none"> SABR: 64.3 Surgery: 54.4 Number of metastases per patient: <ul style="list-style-type: none"> 1 to 5; mean NR 	SABR (n = 42) <ul style="list-style-type: none"> Doses: 60 Gy; 3 fractions × 20 Gy (for all lesions surrounded by lung tissues and that were lying outside of a 2 cm volume surrounding the proximal airways); 5 fractions × 12 Gy (for lesions adjacent to the thoracic wall), 8 fractions × 7.5 Gy (if the whole or part of a lesion was found within the 2 cm volume surrounding the central proximal airways). Equipment: Dedicated stereotactic unit (Novalis, Brainlab, Feldkirchen, Germany) Surgery (n = 68) <ul style="list-style-type: none"> Pulmonary metastasectomy 	Research question: 1 Outcomes <ul style="list-style-type: none"> OS PFS LC Definitions: <ul style="list-style-type: none"> OS = NR PFS = NR LC = Freedom from local progression or recurrence at the treated site as event

3DCRT = 3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; AE = adverse event; ALK = anaplastic lymphoma kinase; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EGFR = estimated glomerular filtration rate; ENRT = elective nodal radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; Gy = gray; IG-VMAT = image-guided volumetric modulated arc therapy; IQR = interquartile range; ITT = intention to treat; LC = lesional control; LCS = local control survival; MDT = metastatic-directed therapy; MV = megavolt; MRI = magnetic resonance imaging; N = node; NA = not applicable; NCI = National Cancer Institute; NIH = National Institutes of Health; NIHR = National Institute for Health Research; NR = not reported; NRS = nonrandomized study; NSCLC = non-small cell lung cancer; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; QoL = quality of life; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria In Solid Tumors; RTOG = Radiation Therapy Oncology Group; SABR = stereotactic ablative radiotherapy; SOC = standard of care; VMAT = volumetric modulated arc therapy.

^a Reported gender as described in the publication.

Figure 3: Number of Included Publications by Publication Year



Note: Some publications reported on the same study.

Appendix 8: Critical Appraisal of Included Studies

Table 18: Risk of Bias Among Randomized Controlled Trials (Cochrane Risk of Bias Tool 250)

First author (publication year) Relevant for clinical research question(s)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Phillips et al. (2020) ⁶³ 1, 2	<p>High risk</p> <p>1.1 (Y). Allocation sequence random using an interactive web response system</p> <p>1.2 (NI). No information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention</p> <p>1.3 (PY). The baseline differences between groups may suggest a problem with the randomization process (Gleason grade higher in the comparator arm versus intervention arm; higher proportion of patients in intervention arm received prior ADT) (PY)</p>	<p>Some concerns</p> <p>2.1 (Y). Participants were aware of their assigned intervention during the trial (open-label)</p> <p>2.2 (Y). Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label)</p> <p>2.3 (NI). No information about whether there were deviations from the intended intervention that arose because of the trial context</p> <p>2.6 (Y). Appropriate analysis used to estimate the effect of assignment to intervention (ITT analysis)</p>	<p>PFS: Low risk</p> <p>AEs: Low risk</p> <p>QoL: Low risk</p> <p>Progression events: Low risk</p> <p>3.1 (Y). Outcome data available for all, or nearly all, participants randomized</p>	<p>PFS: Low risk</p> <p>AEs: Some concerns</p> <p>QoL: Some concerns</p> <p>Progression events: Low risk</p> <p>4.1 (PN). The method of measurement was probably not inappropriate (Kaplan-Meier method used to estimate PFS; CTCAE for AEs)</p> <p>4.2 (PN). It is not likely that the measurement or ascertainment of the outcome had been different between intervention groups</p> <p>4.3 (Y). Outcome assessors were aware of the intervention received by study participants</p> <p>4.4 (PY). The assessment of the outcome probably could have been influenced by knowledge of the intervention received (can be some subjectivity for outcomes that involve assessment of a radiograph or clinical examination based on medical records, such as AE and QoL outcomes)</p> <p>4.5 (PN). It is not likely that the assessment of the outcome was influenced by the knowledge of the intervention received (PN)</p>	<p>Low risk</p> <p>5.1 (PY). Data that produced these results were probably analyzed in accordance with a pre-specified analysis plan</p> <p>The numerical result being assessed was not likely to have been selected, based on results from:</p> <p>5.2 (PN). Multiple eligible outcome measurements within the outcome domain or</p> <p>5.3 (PN). Multiple eligible analyses of the data, based on the a priori protocol</p>	High risk

First author (publication year) Relevant for clinical research question(s)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
<p>SABR-COMET Palma et al. (2019),³² Palma et al. (2020),⁵⁸ Olson et al. (2019)⁵⁹ 1,^{32,58,59} 2^{32,58}</p>	<p>High risk</p> <p>1.1 (Y). Allocation sequence randomized using a computer-generated randomization list with permuted blocks of 9 stratified by the number of metastases (1 to 3 versus 4 to 5)</p> <p>1.2 (NI). No information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention</p> <p>1.3 (PY). The baseline differences between groups may suggest a problem with the randomization process (intervention group had a preponderance of patients with prostate cancer and all the patients had 5 metastases)</p>	<p>Some concerns</p> <p>2.1 (Y). Participants were aware of their assigned intervention during the trial (open label)</p> <p>2.2 (Y). Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open label)</p> <p>2.3 (PN). No major deviations from the intended intervention arose because of the trial context (1 patient from comparator group withdrew consent for further follow-up to pursue SABR)³²</p> <p>2.4 (PY). Probably no imbalance in deviations from intended intervention between groups</p> <p>2.5 (NA).³²</p> <p>2.6 (Y). Appropriate analysis used to estimate the effect of assignment to intervention (ITT analysis)</p>	<p>OS: Low risk</p> <p>PFS: Low risk</p> <p>AEs: Low risk</p> <p>LC: Low risk</p> <p>QoL: Low risk</p> <p>3.1 (Y) Outcome data available for all, or nearly all, participants randomized</p>	<p>OS: Low risk</p> <p>PFS: Low risk</p> <p>AEs: Some concerns</p> <p>LC: Low risk</p> <p>QoL: Some concerns</p> <p>4.1 (PN). The method of measurement was probably not inappropriate (Kaplan-Meier method was used to estimate PFS and OS; CTCAE v.4 used to assess toxicity; FACT-G was used to assess QoL)</p> <p>4.2 (PN). It is not likely that the measurement or ascertainment of the outcome had been different between intervention groups</p> <p>4.3 (NI). No information about whether outcome assessors were aware of the intervention received by study participants</p> <p>4.4 (PY). The assessment of the outcome probably could have been influenced by knowledge of the intervention received (can be some subjectivity for outcomes that involve assessment of a radiograph or clinical examination based on medical records, such as LC, AE, and QoL outcomes)</p> <p>4.5 (PN). It is not likely that the assessment of the outcome was influenced by the knowledge of the intervention received</p>	<p>Low risk</p> <p>5.1 (PY) Data that produced these results were probably analyzed in accordance with a pre-specified analysis plan</p> <p>The numerical result being assessed was not likely to have been selected, based on results from:</p> <p>5.2 (PN). Multiple eligible outcome measurements within the outcome domain or</p> <p>5.3 (PN). Multiple eligible analyses of the data (PN), based on the a priori protocol</p>	<p>High risk</p>

First author (publication year) Relevant for clinical research question(s)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
lyengar et al. (2018) ⁶⁹ 1, 2	<p>Some concerns</p> <p>1.1 (NI). No information about whether allocation sequence was random</p> <p>1.2 (NI). No information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention</p> <p>1.3 (N). The lack of baseline differences between groups does not suggest a problem with the randomization process</p>	<p>Some concerns</p> <p>2.1 (Y). Participants were aware of their assigned intervention during the trial (open-label)</p> <p>2.2 (Y). Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label)</p> <p>2.3 (NI). No information about whether there were deviations from the intended intervention that arose because of the trial context (NI)</p> <p>2.6 (Y). Appropriate analysis used to estimate the effect of assignment to intervention (ITT analysis)</p>	<p>OS: Low risk</p> <p>PFS: Low risk</p> <p>AEs: Low risk</p> <p>Progression events: Low risk</p> <p>3.1 (Y) Outcome data available for all, or nearly all, of the randomized participants</p>	<p>OS: Low risk</p> <p>PFS: Low risk</p> <p>AEs: Some concerns</p> <p>Progression events: Some concerns</p> <p>4.1 (PN). The method of measurement was probably not inappropriate (Kaplan-Meier method was used to estimate PFS and OS)</p> <p>4.2 (PN). It is not likely that the measurement or ascertainment of the outcome been different between intervention groups</p> <p>4.3 (NI). No information about whether outcome assessors were aware of the intervention received by study participants</p> <p>4.4 (PY). The assessment of the outcome probably could have been influenced by knowledge of the intervention received (can be some subjectivity in the assessment of AE outcomes)</p> <p>4.5 (PN). It is not likely that the assessment of the outcome was influenced by the knowledge of the intervention received</p>	<p>Low risk</p> <p>5.1 (PY). Data that produced these results were probably analyzed in accordance with a pre-specified analysis plan</p> <p>The numerical result being assessed was not likely to have been selected, based on results from:</p> <ul style="list-style-type: none"> • 5.2 (PN). Multiple eligible outcome measurements within the outcome domain or • 5.3 (PN). Multiple eligible analyses of the data, based on the a priori protocol 	Some concerns

ADT = androgen deprivation therapy; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.0; FACT-G = Functional Assessment of Cancer Therapy-General; ITT = intention to treat; N = no; NA = not applicable; NI = no information; OS = overall survival; PFS = progression-free survival; PN = probably no; PY = probably yes; QoL = quality of life; SABR = stereotactic ablative radiotherapy; Y = yes.

Table 19: Risk of Bias Among Nonrandomized Studies (RoBANS51,52)

First author (publication year) Relevant for clinical research question(s)	The possibility of the target group comparisons	Target group selection	Confounder	Exposure measurement	Blinding of assessors	Outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias judgment
	Selection bias due to selection of inappropriate comparison target group	Selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group	Selection bias due to inappropriate confounder confirmation and consideration	Performance bias due to inappropriate intervention or inappropriate exposure measurement	Confirmation bias due to inappropriate blinding of assessors	Confirmation bias due to inappropriate outcome assessment methods	Attrition bias due to inappropriate handling of incomplete data	Reporting bias due to selective outcome reporting	
Hurmuz et al. 2020 ⁶⁵ 1	Unclear; patient characteristics of each group were not reported individually	Unclear; unknown whether participants selected from the 10 centres were balanced between groups	Unclear; some confounders were adjusted for PFS, but not for OS	Low; data obtained from medical records	Low; main end points are time-to-event (survival) outcomes	OS: Low PFS: Low Local Progression: Low Outcomes confirmed with medical records	OS: Unclear PFS: Unclear Local Progression: Unclear Unclear if all participant data were included in the analyses	Unclear; no protocol to verify	Some concerns
van de Ven et al. (2020) ⁶⁴ 1	High; groups differ in some of the main characteristics (age, type of metastases, pain)	Low; participant recruitment strategy (standards for inclusion and exclusion and selection method) was the same for both groups	Low; confounders were confirmed and considered during planning and analysis stages	Low; data were obtained from patient records	Low; main end points are time-to-event (survival) outcomes	OS: Low PFS: Low Pain response: Low QoL: Low Outcomes confirmed with medical records	OS: Low PFS: Low Pain response: High QoL: High Not all patient data used in the analysis of QoL (authors excluded all patients with no pain at baseline)	Low; registered protocol a priori with ClinicalTrials.gov (NCT02356497)	High risk

First author (publication year) Relevant for clinical research question(s)	The possibility of the target group comparisons	Target group selection	Confounder	Exposure measurement	Blinding of assessors	Outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias judgment
	Selection bias due to selection of inappropriate comparison target group	Selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group	Selection bias due to inappropriate confounder confirmation and consideration	Performance bias due to inappropriate intervention or inappropriate exposure measurement	Confirmation bias due to inappropriate blinding of assessors	Confirmation bias due to inappropriate outcome assessment methods	Attrition bias due to inappropriate handling of incomplete data	Reporting bias due to selective outcome reporting	
De Bleser et al. (2019)⁶⁶	High; groups differ in some of the main characteristics (use of adjuvant ADT at the time of MDT)	Unclear; unknown whether participants selected from the 15 centres were balanced between groups	Low; confounders were confirmed and considered during planning and analysis stages	Low; data were obtained from patient records from multiple centres	Low; main end points are time-to-event (survival) outcomes	Local progressions: Low AEs: Low Outcomes likely confirmed with medical records	Local progressions: Unclear AEs: Unclear Unclear if all participant data were included in the analyses	Unclear; no protocol to verify	High risk
He et al. (2018)⁶⁷ 1, 2	Low; no statistical differences between groups in pre-treatment clinical characteristics	Low; participant recruitment strategy (standards for inclusion and exclusion and selection method) was the same for both groups	Unclear; unclear whether confounders were confirmed and considered during planning and analysis stages for OS outcome	Low; data were obtained from patient records	Low; main end points are time-to-event (survival) outcomes	OS: Low AEs: Low Outcomes likely confirmed with medical records	OS: Unclear AEs: Unclear Unclear if all participant data were included in the analyses	Unclear; no protocol to verify	Some concerns

First author (publication year) Relevant for clinical research question(s)	The possibility of the target group comparisons	Target group selection	Confounder	Exposure measurement	Blinding of assessors	Outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias judgment
	Selection bias due to selection of inappropriate comparison target group	Selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group	Selection bias due to inappropriate confounder confirmation and consideration	Performance bias due to inappropriate intervention or inappropriate exposure measurement	Confirmation bias due to inappropriate blinding of assessors	Confirmation bias due to inappropriate outcome assessment methods	Attrition bias due to inappropriate handling of incomplete data	Reporting bias due to selective outcome reporting	
Filippi et al. (2016)⁶⁸ 1, 2	High; groups differ in some of the main characteristics (age, period of treatment)	Low; participant recruitment strategy (standard inclusion and exclusion selection method) was the same for both groups	Low; confounders were confirmed and considered during planning and analysis stages	Low; data were obtained from patient records	Low; main end points are time-to-event (survival) outcomes	OS: Low PFS: Low AEs: Low Progressions: Low Outcomes confirmed with medical records	OS: Low PFS: Low AEs: Low Progressions: Low No missing data in the analyses of all outcomes	Unclear; no protocol to verify	High risk
Widder et al. (2013)⁶⁰ and Lodeweges et al. (2017)⁶¹ 1, 2	High; groups differ in some of the main characteristics (age, primary tumour, metastasis-free interval, prior chemotherapy)	Unclear; participant recruitment strategy (selection method) not clearly described	Low; confounders were confirmed and considered during planning and analysis stages	Low; data were obtained from patient records	Low; main end points are time-to-event (survival) outcomes	OS: Low PFS: Low LC: Low Outcomes likely confirmed with medical records	OS: Low PFS: Low LC: Low No missing data in the analyses of all outcomes	Unclear; no protocol to verify	High risk

ADT = androgen deprivation therapy; AE = adverse event; LC = lesional control; MDT = metastatic-directed therapy; OS = overall survival; PFS = progression-free survival; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; QoL = quality of life.

Appendix 9: Main Study Findings

Table 20: Overall Survival

First author (publication year)	Treatments (Intervention vs. comparator) Follow-up	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			1-year	2-year	3-year	4-year	5-year			
RCTs										
SABR-COMET Palma et al. (2019) ³² and Palma et al. (2020) ⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy alone (n = 33) Short-term Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • Systemic therapy: 25 (19 to 54) months ³² Long-term Median F/U (IQR): Total: 51 (46 to 58) months ⁵⁸	Short-term F/U: 24 vs. 16 Long-term F/U: 35 vs. 24	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short-term F/U: NR Long-term F/U: 42.3 (28 to 56) vs. 17.7 (6 to 34)	Short-term F/U: 41 (26 to not reached) vs. 28 (19 to 33) Long-term F/U: 50 (29 to 83) vs. 28 (18 to 39)	Short-term F/U: 0.57 (0.30 to 1.10); P = 0.09 Long-term F/U: 0.47 (0.27 to 0.81); P = 0.006	Short and long-term F/U: NR
Authors' conclusions: "In patients with a controlled primary tumour and one to five oligometastases, SABR is associated with a 13-month increase in overall survival. With extended follow-up, the impact of SABR on OS was larger in magnitude than in the initial analysis and durable over time." ³²										
Iyengar et al. (2018) ⁶⁹	SABR + chemotherapy (n = 14) vs. chemotherapy alone (n = 15) Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	NR	NR	NR	NR	NR	NR	Not reached (NR) vs. about 1 year without crossover; 17 months with crossover (NR)	NR	NR
Authors' conclusions: "Median OS was not reached for the SABR plus maintenance chemotherapy arm, though the study was not powered to show a statistical difference in survival." ⁶⁹										

First author (publication year)	Treatments (Intervention vs. comparator) Follow-up	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			1-year	2-year	3-year	4-year	5-year			
NRSSs										
Hurmuz et al. (2020) ⁶⁵	SABR ± hormonotherapy (n = 129) vs. conventional fractionation radiotherapy ± hormonotherapy (n = 47) Median F/U (IQR): Total: 22.9 (3.3 to 77.8) months	NR	NR	87.7 (NR) vs. 87.3 (NR); P = 0.91	NR	NR	NR	NR	NR	NR
Authors' conclusions: "There was no significant difference in OS between patients treated with SBRT and conventional fractionation." ⁶⁵										
van de Ven et al. (2020) ⁶⁴	SABR (n = 65) vs. 3DCRT (n = 66) Median F/U (IQR): • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months	3 months: 2 vs. 5; 6 months: 4 vs. 13; 12 months: 6 vs. 20	85 (NR) vs. 65 (NR)	NR	NR	NR	NR	Not reached (NR) at 18 months; P < 0.0001 vs. NR	0.44 (0.24 to 0.81); P = NR	NR
Authors' conclusions: "OS survival rates were significantly better in the SBRT group, which is probably largely due to selection of patients, and confirmed by the differences in baseline between the two treatment groups." ⁶⁴										
He et al. (2018) ⁶⁷	SABR (n = 11) vs. 3DCRT (n = 15) Median F/U: Total: 13 months	NR	68.2 (NR) vs. 55.8 (NR)	40.9 (NR) vs. 16.0 (NR)	20.5 (NR) vs. 0.0 (NR)	NR	NR	20 (NR) vs. 14 (NR)	0.61 (0.23 to 1.65); P = 0.323	NR
Authors' conclusions: "The slightly better overall survival...in the stereotactic body radiation therapy group in comparison to the conformal radiation therapy group...is insignificant." ⁶⁷ The authors acknowledged that the OS results might be affected by study's limitations, i.e., small sample size, differences in study and patient characteristics between groups, and the lack chemotherapy after SABR or RTRT.										
Filippi et al. (2016) ⁶⁸	SABR (n = 28) vs. surgery (n = 142) Median F/U (IQR): • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months	10 vs. 37	89 (70 to 96) vs. 96 (92 to 99)	77 (56 to 89) vs. 82 (74 to 87)	NR	NR	NR	NR	1.7 (0.84 to 3.43); P = 0.139	1.71 (0.82 to 3.54); P = 0.149
Authors' conclusions: "Patients treated with SBRT for CRC lung oligometastases could achieve overall survival rates at 2 years comparable with surgery." ⁶⁸										

First author (publication year)	Treatments (Intervention vs. comparator) Follow-up	Death events; n	OS rate, % (95% CI)					Median OS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			1-year	2-year	3-year	4-year	5-year			
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ^{61a}	SABR (n = 42) vs. surgery (PME) (n = 68) Short-term F/U: Median F/U (IQR): Total: 43 (36 to 60) months ⁶⁰ Long-term F/U: Median F/U (IQR): Total: 91.2 (69.6 to 117.6) months ⁶¹	Short-term F/U: 17 vs. 35 Long-term F/U: NR	Short- and long-term F/U: 98 (84 to 100) vs. 87 (76 to 93)	Short- and long-term F/U: 86 (71 to 93) vs. 74 (61 to 82)	Short-term F/U: 60 (42 to 73) vs. 62 (49 to 73) Long-term F/U: 64 (48 to 77) vs. 63 (51 to 73)	Short-term F/U: 60 (42 to 73) vs. 47 (33 to 59) Long-term F/U: 57 (41 to 70) vs. 50 (38 to 61)	Short-term F/U: 49 (25 to 69) vs. 41 (27 to 54) Long-term F/U: 45 (30 to 59) vs. 41 (29 to 53)	Short- and long-term F/U: NR	Short-term F/U: 0.79 (0.43 to 1.42); P = 0.427 Long-term F/U: 1.11 (0.70 to 1.75); P = NR; NS	Short-term F/U: NR Long-term F/U: 0.76 (0.38 to 1.54); P = NR; NS
Authors' conclusions: "Although SABR was second choice after PME, survival after PME was not better than after SABR." ⁶⁰										

3DCRT = 3-dimensional conformal radiation therapy; adj = adjusted; CI = confidence interval; CRC = colorectal cancer; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; NR = not reported; NS = non-significant; OS = overall survival; PME = pulmonary metastasectomy; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiation therapy; unadj = unadjusted; vs. = versus.

^a OS rates at 6, 7, and 8 years for SABR vs. surgery (PME) were 35% (95% CI, 21% to 50%) vs. 37% (95% CI, 26% to 48%), 29% (95% CI, 16% to 44%) vs. 35% (95% CI, 24% to 46%), and 13% (95% CI, 3% to 30%) vs. 35% (95% CI, 24% to 46%), respectively.

Table 21: Progression-Free Survival

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Progression events; n	PFS rate, % (95% CI)						Median PFS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
RCTs											
Phillips et al. (2020) ⁶³	SABR (n = 36) vs. observation (n = 18) Median F/U (IQR): Total: 18.8 (5.8 to 35.0) months	7 vs. 11; P = 0.005	19 (9.6 to 35.4) vs. 61 (38.5 to 79.6)	NR	NR	NR	NR	NR	Not reached (NR) vs. 5.8 (NR)	0.3 (0.11 to 0.81); P = 0.002	NR
Authors' conclusions: "SABR is a safe and effective modality for metastases-directed therapy in oligometastatic prostate cancer that improves PFS compared with observation and results in a systemic adaptive immune response." ⁶³											
SABR-COMET Palma et al. (2019) ³² Palma et al. (2020) ⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy alone (n = 33) Short-term Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • Systemic therapy: 25 (19 to 54) months ³² Long-term Median F/U (IQR): Total: 51 (46 to 58) months ⁵⁸	Short-term F/U: 39 vs. 28 Long-term F/U: 45 vs. 29	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short-term F/U: NR Long-term F/U: 21.6 (12 to 33) vs. 3.2 (0 to 14)	Short-term F/U: NR Long-term F/U: 17.3 (8 to 30) vs. 0 (NA)	12 (6.9 to 30.4) vs. 6.0 (3.4 to 7.1) Long-term F/U: 11.6 (6.1 to 23.4) vs. 5.4 (3.2 to 6.8)	0.47 (0.30 to 0.76); P = 0.0012 Long-term F/U: 0.48 (0.31 to 0.76); P = 0.001	Short- and long-term F/U: NR
Authors' conclusions: "In patients with a controlled primary tumour and one to five oligometastases, SABR is associated with... a doubling of progression-free survival." ³²											
Iyengar et al. (2018) ⁶⁹	SABR + chemotherapy (n = 14) vs. chemotherapy (n = 15) Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	4 vs. 10	NR	NR	NR	NR	NR	NR	9.7 (NR) vs. 3.5 (NR)	0.304 (0.113 to 0.815); P = 0.01	NR
Authors' conclusions: "Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone." ⁶⁹											

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Progression events; n	PFS rate, % (95% CI)						Median PFS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
NRSs											
Hurmuz et al. (2020)⁶⁵	SABR ± hormonotherapy (n = 129) vs. conventional fractionation radiotherapy ± hormonotherapy (n = 47) Median F/U (IQR): Total: 22.9 (3.3 to 77.8) months	NR	NR	86.2 (NR) vs. 54.9 (NR); P < 0.001	NR	NR	NR	NR	NR	NR	0.26 (0.13 to 0.55); P < 0.001
Authors' conclusions: "2-year PFS was significantly better in patients treated with SBRT to the oligometastatic site than those treated with conventional fractionation." ⁶⁵											
van de Ven et al. (2020)⁶⁴	SABR (n = 65) vs. 3DCRT (n = 66) Median F/U (IQR): SABR: 25 (5 to 52) months 3DCRT: 46 (9 to 55) months	NR	NR	54 (NR) vs. 19 (NR)	NR	NR	NR	NR	12 (NR) vs. 5 (NR); P = 0.002	0.63 (0.41 to 0.95); P = NR	NR
Authors' conclusions: "PFS survival rates were significantly better in the SBRT group, which is probably largely due to selection of patients, and confirmed by the differences in baseline between the 2 treatment groups." ⁶⁴											
Filippi et al. (2016)⁶⁸	SABR (n = 28) vs. surgery (n = 142) Median F/U (IQR): SABR: 27 (16.1 to 71.7) months Surgery: 45.8 (13.6 to 107.1) months	21 vs. 87	NR	NR	NR	NR	NR	NR	NR	2.44 (1.51 to 3.94); P < 0.001	2.78 (1.67 to 4.62); P < 0.001
Authors' conclusions: "..., both Kaplan-Meier functions and Cox models indicated a worse prognosis in terms of PFS for the SBRT cohort. However, much of this effect seems to be attributable to the more intensive follow-up protocol applied after SBRT." ⁶⁸											

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Progression events; n	PFS rate, % (95% CI)						Median PFS (95% CI); months	Unadj HR (95% CI)	Adj HR (95% CI)
			6-month	1-year	2-year	3-year	4-year	5-year			
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ⁶¹	SABR (n = 42) vs. surgery (PME) (n = 68) Short-term Median F/U (IQR): Total: 43 (36 to 60) months ⁶⁰ Long-term Median F/U (IQR): Total: 91.2 (69.6 to 117.6) months ⁶¹	Short-term F/U: 32 vs. 51 Long-term F/U: NR	Short- and long- term F/U: NR	Short- term F/U: 50 (34 to 64) vs. 54 (42 to 65) Long- term F/U: 49 (34 to 63) vs. 56 (43 to 66)	Short- term F/U: 21 (9 to 35) vs. 33 (22 to 45) Long- term F/U: 27 (14 to 41) vs. 35 (23 to 46)	Short- term F/U: 8 (2 to 22) vs. 22 (12 to 33) Long- term F/U: 18 (8 to 32) vs. 26 (16 to 36)	Short- term F/U: 8 (2 to 22) vs. 18 (9 to 30) Long- term F/U: 18 (8 to 32) vs. 20 (11 to 30)	Short- and long-term F/U: NR	Short- and long-term F/U: NR	Short- and long-term F/U: NR	
Authors' conclusions: No specific conclusion regarding PFS was provided.											

3DCRT = 3-dimensional conformal radiation therapy; adj = adjusted; CI = confidence interval; ENRT = elective nodal radiotherapy; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; NA = not applicable; NR = not reported; PFS = progression-free survival; PME = pulmonary metastasectomy; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiation therapy; unadj = unadjusted; vs. = versus.

^a PFS rates at 6, 7, and 8 years for SABR vs. surgery (PME) for all time points were 18% (95% CI, 8% to 32%) vs. 20% (95% CI, 11% to 30%).

Table 22: Health-Related QoL

First author (publication year) Follow-up	Tools and definitions	Results
RCTs		
Phillips et al. (2020) ⁶³	QoL • Brief Pain Inventory (Short Form)	QoL • Data not provided
<p>Authors' conclusions: "No differences in Brief Pain Inventory (Short Form) scores were observed between arms or within either arm across time."⁶³</p>		
<p>SABR-COMET</p> <p>Palma et al. (2019),³² Palma et al. (2020),⁵⁸ Olson et al. (2019)⁵⁹</p> <p>Short-term median F/U (IQR):</p> <ul style="list-style-type: none"> • SABR + systemic therapy: 26 (23 to 37) months • Systemic therapy: 25 (19 to 54) months^{32,59} <p>Long-term median F/U (IQR):</p> <p>Total: 51 (46 to 58) months⁵⁸</p>	QoL • FACT-G (4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being)	<p>QoL: SABR + systemic therapy versus systemic therapy</p> <p>FACT-G at 6 months, mean (SD)^{a,32}</p> <ul style="list-style-type: none"> • Total scores (sum of FACT-G physical, social, emotional and functional well-being subscales): 82.6 (16.6) versus 82.5 (16.4); P = 0.99 <p>FACT-G subscales, mean (SD):</p> <ul style="list-style-type: none"> • Physical: 22.4 (4.8) versus 23.1 (4.9); P = 0.54 • Social: 22.8 (5.1) versus 21.8 (6.3); P = 0.48 • Emotional: 18.1 (5.1) versus 18.3 (4.3); P = 0.87 • Functional: 19.4 (5.8) versus 18.8 (7.0); P = 0.74 <p>FACT-G over 42 months:⁵⁹</p> <ul style="list-style-type: none"> • Total score: P = 0.42 • Physical: P = 0.98 • Functional: P = 0.59 • Emotional: P = 0.82 • Social: P = 0.17 <p>FACT-G over 5 years⁵⁸</p> <ul style="list-style-type: none"> • Total score: P = 0.98 • Physical: P = 0.72 • Functional: P = 0.47 • Emotional: P = 0.77 • Social: P = 0.19
<p>Authors' conclusions: "There were no significant differences in overall mean FACT-G scores at 6 months, or in any of the physical, social, functional, or emotional QoL subscales."³² "The use of SABR, compared with standard of care, was not associated with a QoL detriment. This suggests that broad QoL changes are due to underlying disease processes over time. Future research could further explore site- and tumour-specific QoL measures and their ability to detect more subtle changes over time and differences between treatment options. We believe this work supports future clinical trials that are histology and site specific."⁵⁹ "The long-term analysis of FACT-G scores over time are shown in Figure 3, with no differences in total QoL scores, or subscale score."⁵⁸</p>		
NRS		
van de Ven et al. (2020) ⁶⁴	Pain Pain scores and response were assessed only in patients who reported pain at baseline Pain response Defined according to international consensus criteria using NRS and Brief	Pain Number of patients with pain at baseline: • SBRT: n = 38; 3DCRT: n = 57 Mean (SD) NRS scores at baseline: • SBRT: 3.0 (3.5); 3DCRT: 4.6 (3.3) Pain response:
<p>Median F/U (IQR):</p> <ul style="list-style-type: none"> • SABR: 25 (5 to 52) months • 3DCRT: 46 (9 to 55) months 		

First author (publication year) Follow-up	Tools and definitions	Results
	<p>Pain Inventory scores; information on pain medication and daily oral morphine equivalent based on returned QoL questionnaires or gathered during follow-ups</p> <p>Partial response = a pain reduction of at least 2 points without an increase in analgesic use, or at least a 25% reduction in opioid use without an increase in pain score</p> <p>Complete response = a pain score of 0 without an increase in analgesic use</p> <p>Pain progression = an increase in pain score of 2 or more points above baseline with no change in analgesic use, or an increase in pain score of 1 point above baseline with an increase in analgesic use of 25% or more</p> <p>Stable pain = no change in pain score or analgesic use</p> <p>Intermediate response = all other responses that do not fit under partial response, complete response, pain progression, or stable pain</p> <p>Responders = complete or partial response was achieved on at least 1 of the follow-up time points</p> <p>Duration of pain response = time until pain progression, intermediate pain response, stable pain, or death</p> <p>Ongoing pain response = a continuous pain response (e.g., partial or complete) 1 year after treatment</p> <p>QoL tools (global, functional, and role scales)</p> <p>EORTC QLQ-BM22, EORTC QLQ-C15-PAL, Brief Pain Inventory, EQ-5D; validated tools used</p>	<ul style="list-style-type: none"> • SBRT: 84% (n = 32); 3DCRT: 81% (n = 46); P = 0.79 <p>Complete response:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 16% (n = 4); 3DCRT: 25% (n = 10); P = 0.359 • 6 months – SBRT: 34.6% (n = 9); 3DCRT: 19.4% (n = 6); P = 0.180 • 12 months – SBRT: 40% (n = 4); 3DCRT: 15.4% (n = 4); P = 0.119 <p>Partial response</p> <ul style="list-style-type: none"> • 3 months – SBRT: 56% (n = 14); 3DCRT: 42.5% (n = 17) • 6 months – SBRT: 34.6% (n = 9); 3DCRT: 41.9% (n = 13) • 12 months – SBRT: 40% (n = 4); 3DCRT: 34.6% (n = 9) <p>Pain progression:</p> <ul style="list-style-type: none"> • 3 months – SBRT: 24% (n = 6); 3DCRT: 17.5% (n = 7) • 6 months – SBRT: 11.5% (n = 3); 3DCRT: 29% (n = 9) • 12 months – SBRT: 10% (n = 1); 3DCRT: 15.4% (n = 4) <p>Intermediate responses + stable responses:</p> <ul style="list-style-type: none"> 3 months – SBRT: 4.2% (n = 1); 3DCRT: 15% (n = 6) 6 months – SBRT: 19.2% (n = 5); 3DCRT: 9.7% (n = 3) 12 months – SBRT: 10% (n = 1); 3DCRT: 34.6% (n = 9) <p>Responders:</p> <ul style="list-style-type: none"> 3 months – SBRT: 72% (n = 18); 3DCRT: 67.5% (n = 27); P = 0.702 6 months – SBRT: 69% (n = 18); 3DCRT: 60% (n = 19); P = 0.502 12 months – SBRT: 80% (n = 8); 3DCRT: 50% (n = 13); P = 0.04 <p>Median duration of pain response (range):</p> <ul style="list-style-type: none"> SBRT: 24 weeks (0 to 50) 3DCRT: 23 weeks (1 to 58); P = 0.79 <p>Ongoing pain response:</p> <ul style="list-style-type: none"> 6 months – SBRT: 65%; 3DCRT: 61%; P = 0.79 12 months – SBRT: 50%; 3DCRT: 42%; P = 0.77 <p>Re-irradiation for pain recurrence or progression:</p> <ul style="list-style-type: none"> SBRT: 5% 3DCRT: 33.3%; P < 0.05 <p>QoL (where P values of < 0.01 were considered statistically significant for mixed models)</p> <p>No significant differences between groups for any QoL subscales</p>

First author (publication year) Follow-up	Tools and definitions	Results
Authors' conclusions: "In patients with oligometastatic disease, SBRT to bone metastases did not improve pain response or QoL compared with 3DCRT. Reirradiation was less often needed in the SBRT group." ⁶⁴		

3DCRT = 3-dimensional conformal radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Bone Metastasis 22; EORTC QLQ-C15-PAL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative; EQ-5D = EuroQol 5-Dimensions questionnaire; FACT-G = Functional Assessment of Cancer Therapy-General; F/U = follow-up; IQR = interquartile range; NRS = numeric rating scale; QoL = quality of life; SABR = stereotactic ablative radiotherapy.

^a Baseline values were not reported numerically, but graphically instead.

Table 23: Lesional Control

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Local progression events; n	Crude LC rate, % (95% CI)	LC rate, % (95% CI)						Median LC (95% CI); months	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
				1-year	2-year	3-year	4-year	5-year	6-year			
RCTs												
SABR-COMET Palma et al. (2019)³² Palma et al. (2020)⁵⁸	SABR + systemic therapy (n = 66) vs. systemic therapy (n = 33) Short-term Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • systemic therapy: 25 (19 to 54) months ³² Long-term Median F/U (IQR): Total: 51 (46 to 58) months ⁵⁸	Short- and long-term F/U: NR	Short-term F/U: 75 (NR) vs. 49 (NR); P = 0.0010 Long-term F/U: 63 (NR) vs. 46 (NR); P = 0.039	NR	NR	NR	NR	NR	NR	NR	NR	NR
<p>Authors' conclusions: "The proportion of patients with lesional control (i.e., the absence of progression in the lesions initially present of randomization) was 49% (28 of 57 assessable lesions) in the control group and 75% (75 of 100 assessable lesions) in the SABR group (p=0.0010), represented by an absolute increase of 26% (95% CI 10–41)" (p. 2055).³²</p> <p>"The overall long-term LC rate, defined as the absence of progression in the lesions initially present at random assignment on the basis of RECIST version 1.1, was 46% (26 of 57 assessable lesions) in the control arm and 63% (65 of 104 assessable lesions in the SABR arm (P = .039), corresponding to an absolute increase of 17% (95% CI, 1% to 33%)" (p. 4).⁵⁸</p>												
Iyengar et al. (2018)⁶⁹	SABR + chemotherapy (n = 14) vs. chemotherapy (n = 15) Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	0 vs. 7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Authors' conclusions: No specific conclusion provided.												

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Local progression events; n	Crude LC rate, % (95% CI)	LC rate, % (95% CI)						Median LC (95% CI); months	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
				1-year	2-year	3-year	4-year	5-year	6-year			
NRSs												
De Bleser et al. (2019) ⁶⁶	SABR (n = 309) vs. ENRT (n = 197) Median F/U (IQR): Total: 36 (23 to 56) months	50 vs. 9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Authors' conclusions: No specific conclusion provided.												
Hurmuz et al. (2020) ⁶⁵	SABR ± hormonotherapy; n = 129 vs. conventional fractionation radiotherapy ± hormonotherapy; n = 47 Median F/U (IQR): Total: 22.9 (3.3 to 77.8) months	2 vs. 7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Authors' conclusions: No specific conclusion provided.												
Filippi et al. (2016) ⁶⁸	SABR (n = 28) vs. surgery (n = 142) Median F/U (IQR): • SABR: 27 (16.1 to 71.7) months • Surgery: 45.8 (13.6 to 107.1) months	6 vs. 6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Authors' conclusions: No specific conclusion provided.												

First author (publication year)	Treatments (intervention vs. comparator) Follow-up	Local progression events; n	Crude LC rate, % (95% CI)	LC rate, % (95% CI)						Median LC (95% CI); months	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
				1-year	2-year	3-year	4-year	5-year	6-year			
Widder et al. (2013) ⁶⁰ and Lodeweges et al. (2017) ^{61a}	SABR (n = 42) vs. surgery (PME) (n = 68) Short-term F/U Median F/U (IQR): Total: 43 (36 to 60) months ⁶⁰ Long-term F/U Median F/U (IQR): Total: 91.2 (69.6 to 117.6) months ⁶¹	Short- and long-term F/U: NR	NR	Short-term F/U: 94 (79 to 99) vs. 93 (83 to 97) Long-term F/U: 95 (80 to 99) vs. 93 (83 to 97)	Short-term F/U: 94 (79 to 99) vs. 90 (78 to 96) Long-term F/U: 95 (80 to 99) vs. 91 (79 to 96)	Short-term F/U: 85 (55 to 96) vs. 83 (65 to 92) Long-term F/U: 90 (70 to 97) vs. 85 (70 to 93)	Short-term F/U: 85 (55 to 96) vs. 83 (65 to 92) Long-term F/U: 90 (70 to 97) vs. 85 (70 to 93)	Short-term F/U: NR Long-term F/U: 83 (57 to 94) vs. 81 (65 to 90)	Short-term F/U: NR Long-term F/U: 83 (57 to 94) vs. 81 (65 to 90)	Short- and long-term F/U: NR	NR Long-term F/U: 0.8 (0.24 to 2.65)	Short- and long-term F/U: NR

Authors' conclusions: "Patterns of progressions and post-treatment management did not differ between SABR and PME" (p. 411).⁶⁰

CI = confidence interval; ENRT = elective nodal radiotherapy; F/U = follow-up; HR = hazard ratio; IQR = interquartile range; LC = lesional control; NR = not reported; PME = pulmonary metastasectomy; RCT = randomized controlled trial; SABR = stereotactic ablative radiotherapy; vs. = versus.

^a LC rates at 7 and 8 years for SABR vs. surgery (PME) for both time points was 83% (95% CI, 57% to 94%) vs. 81% (95% CI, 65% to 90%).

Table 24: Adverse Events

First author (Publication year) Follow-up	Tools	Results
RCTs		
Phillips et al. (2020)⁶³ Median F/U (IQR): Total: 18.8 (5.8 to 35.0) months	CTCAE v4.0	Number of patients with AEs New grade 1 AEs at 90 days: • SABR: 29/36 (81%) versus observation: 12/16 (75%) New grade 1 AEs at 180 days: • SABR: 15/36 (42%) versus observation: 3/11 (27%) New grade 2 AEs at 90 days: • SABR: 3/36 (8%) versus observation: 0/16 (0) New grade 2 AEs at 180 days: • SABR: 2/36 (6%) versus observation: 0/11 (0) Grade 3 or higher AEs: None
Authors' conclusions: "The adverse effects associated with SABR were mild and did not appear to affect quality of life."		
SABR-COMET Palma et al. (2019),³² Palma et al. (2020)⁵⁸ Short-term Median F/U (IQR): • SABR + systemic therapy: 26 (23 to 37) months • systemic therapy: 25 (19 to 54) months ³² Long-term Median F/U (IQR): Total: 51 (46 to 58) months⁵⁸	CTCAE v4.0	Number of patients with AEs AE grade ≥ 2: • SABR + systemic therapy: 61% (n = 40) versus systemic therapy: 46% (n = 15); P = 0.15 Treatment-related AE grade ≥ 2: • SABR + systemic therapy: 29% (n = 19) versus systemic therapy: 9% (n = 3); P = 0.026 with an absolute increase of 20% (95% CI, 5 to 34) Death (grade 5): • SABR + systemic therapy: 4.5% (n = 3; radiation pneumonitis [n = 1], pulmonary abscess [n = 1], and subdural hemorrhage after surgery to repair a SABR-related perforated gastric ulcer [n = 1]) versus systemic therapy: 0% (n = 0); P = 0.55 Fatigue (grade 2): • SABR + systemic therapy: 6% (n = 4) versus systemic therapy: 6% (n = 2); P = 0.45 Fatigue (grade 3): • SABR + systemic therapy: 0% (n = 0) versus systemic therapy: 3% (n = 1); P = 0.45 Dyspnea (grade 2): • SABR + systemic therapy: 2% (n = 1) versus systemic therapy: 0% (n = 0); P = 1.00 Dyspnea (grade 3): • SABR + systemic therapy: 2% (n = 1) versus systemic therapy: 0% (n = 0); P = 1.00 Pain (any type, including muscle, bone, and other; grade 2) • SABR + systemic therapy: 8% (n = 5) versus systemic therapy: 0% (n = 0); P = 0.14 Pain (any type, including muscle, bone, and other; grade 3) • SABR + systemic therapy: 5% (n = 3) versus systemic therapy: 0% (n = 0); P = 0.14
Authors' conclusions: "SABR was associated with an improvement in overall survival, meeting the primary end point of this trial, but 3 (4–5%) of 66 patients in the SABR group had treatment-related death." ³² ; "There were no new safety signals, and SABR had no detrimental impact on QoL." ⁵⁸		

First author (Publication year) Follow-up	Tools	Results
Iyengar et al. (2018)⁶⁹ Median F/U (IQR): Total: 9.6 (2.4 to 30.2) months	CTCAE v4.0	Toxicity (number of events) Grade 1: • SABR + maintenance: 13 versus maintenance only: 17 Grade 2: • SABR + maintenance: 5 versus maintenance only: 5 Grade 3: • SABR + maintenance: 4 versus maintenance only: 2 Grade 4: • SABR + maintenance: 0 versus maintenance only: 1 Grade 5: • SABR + maintenance: 3 versus maintenance only: 6
Authors' conclusions: "Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone, with no difference in toxic effects." ⁶⁹		
NRSs		
De Bleser et al. (2019)⁶⁶ Median F/U (IQR): Total: 36 (23 to 56) months	CTCAE or RTOG grading system	Number of patients with AEs Grade 3 or higher in both early and late toxicity • SABR: 0 (0%) • ENRT: 5 (2.5%); P = 0.009 Early toxicity of all grades: • SABR: 3 (1%) • ENRT: 12 (6%); P = 0.002 Late toxicity of all grades: • SABR: 16 (5%) • ENRT: 31 (16%); P < 0.001
Authors' conclusions: "ENRT reduces the number of nodal recurrences as compared with SBRT, however at higher toxicity." ⁶⁶		
He et al. (2018)⁶⁷ Median F/U: Total: 13 months	CTCAE v3.0 or RTOG	Liver toxicity: • SABR: One patient had grade 1 to 2; 1 patient had grade 3 • 3DCRT: Three patients had grade 1 and 2; 2 patients had grade 3 Hepatic toxicity-inducing rate: • No difference between groups (P = 0.674)
Authors' conclusions: "Non-invasive radiation therapy provides satisfactory survival benefit for limited colorectal cancer liver metastases without intolerable toxicity and is therefore especially suitable for those elderly patients with poor performance status." ⁶⁷		

First author (Publication year) Follow-up	Tools	Results
Filippi et al. (2016) ⁶⁸ Median F/U (IQR): SABR: 27 (16.1 to 71.7) months Surgery: 45.8 (13.6 to 107.1) months	CTCAE v3.0	Number of patients with AEs SABR: <ul style="list-style-type: none"> • Pulmonary toxicity – grade 0: 64.2% (n = 18); grade 1: 21.4% (n = 6); grade 2: 14.4% (n = 4) • Radiological lung toxicity – grade 0: 39.2% (n = 11); grade 1: 17.8% (n = 5); grade 2: 28.6% (n = 8); grade 3: 14.4% (n = 4) • Chronic chest wall pain – grade 2: 3.6% (n = 1); grade 3: 3.6% (n = 1) • Skin toxicity – grade 2: 3.6% (n = 1) Surgery: <ul style="list-style-type: none"> • Death: 0.7% (n = 1) within 30 days
Authors' conclusions: No specific conclusions for AEs.		

3DCRT = 3-dimensional conformal radiation therapy; AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; ENRT = elective nodal radiotherapy; F/U = follow-up; IQR = interquartile range; NSCLC = non-small cell lung cancer; PFS = progression-free survival; QoL = quality of life; SABR = stereotactic ablative radiotherapy; RCT = randomized controlled trial; SBRT = stereotactic body radiotherapy; NRS = nonrandomized study; RTOG = Radiation Therapy Oncology Group.

Table 25: Patient and Public Involvement in CADTH's SABR for the Treatment of Oligometastatic Cancer HTA

Topic	Item	Reported on page
1: Aim	A patient with experience with SABR was involved in developing the protocol and commenting on the findings. This patient, and other patient stakeholder groups (Canadian Partnership Against Cancer, Canadian, Canadian Cancer Survivor Network) were invited to provide feedback on the draft of the baseline clinical review.	26, 27
2: Methods	We engaged one patient with oligometastatic cancer (primary head and neck cancer with a lung metastasis) that was treated with SABR. An oncology trialist identified this individual as a patient collaborator. After giving informed consent, the patient collaborator discussed their experience of SABR treatment via teleconference and email communication. Once preliminary findings from the review were available, the patient was invited to give their perceptions of key findings, including whether the findings are understandable, and if they reflect their experiences.	27
3: Study results	In their discussions, the researchers were made aware of the importance of three outcomes in particular: overall survival, progression-free survival, and quality of life, especially with regards to breathing problems and fatigue. They mentioned being able to exercise/be active was important to them. They mentioned satisfaction in being able to return to work after SABR treatment. The involvement of a patient prompted the research team to discuss which adverse effects of SABR were of concern to the patient collaborator. Pain and fatigue were mentioned and reported in the results where available. Sharing these concerns allowed the research team to consider the evidence in the context of the wider experiences of patients and caregivers when preparing the assessment.	62, 63

Topic	Item	Reported on page
4: Discussion and conclusions	<p>Success of patient involvement in this report is related to several factors. First, the patient partners are briefed on the objectives of the project and their role. Second, they are supported by experienced Patient Engagement Officers who can facilitate the use of their involvement with the research team.</p> <p>Established processes are in place, and our patient collaborator was offered compensation for their time to participate in the project.</p> <p>However, there were limitations. The topic and research questions were already determined before engaging the patient collaborator. Due to time constraints, our collaborator and other patient stakeholders were invited to participate within a set time frame, and with a deadline for providing feedback.</p>	65, 66
5: Reflections and critical perspective	<p>Our patient collaborator was highly engaged in the conversation with researchers. They had clear opinions and concerns during the teleconference. They reported family-borne costs or burdens such as travel that was covered by private insurance. Although not within the scope of this report, the conversation of patient-borne costs and experiences of travelling for treatment helped the researchers appreciate the reality of receiving SABR treatment.</p> <p>Ethical and equity issues are sometimes revealed in the telling of their experiences. For example, our patient collaborator lived in a northern, rural location. It was 1200 km to the largest cancer centre where the treatment plan was made, and a PET scan performed. They were able to receive treatment 450 km from home at a regional cancer centre. They sometimes needed a family member to travel with them. They stayed in housing for patients and families located near the cancer centre for the duration of their treatment. Many of their costs were covered by their private insurance plan through work. These comments allowed the researchers to reflect on geographic barriers to accessing services, as well as additional patient considerations when travelling for treatment.</p> <p>Some limitations of our patient engagement are that people often have concerns that are not part of the project scope (e.g., accessing diagnosis, difficulty finding a knowledgeable health care provider), but the topic and question are already identified when the project begins.</p> <p>It can be difficult to identify a patient whose experience is similar to the population of interest.</p> <p>The timeframe of the project makes it difficult for patients to participate fully, on terms that work for them (e.g., daytime teleconferences). People need access to reliable technology, phone, and internet to participate, possibly excluding some voices.</p>	66, 67

HTA = Health Technology Assessment; PET = positron emission tomography; SABR = stereotactic ablative radiotherapy.