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CADTH HEALTH TECHNOLOGY ASSESSMENT

Stereotactic Ablative Radiotherapy for the Treatment of Oligometastatic Cancer — Project Protocol

PROSPERO REGISTRATION NUMBER: CRD42020167767

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Cite As: Stereotactic Ablative Radiotherapy for the Treatment of Oligometastatic Cancer. Ottawa: CADTH: 2020 Apr. (CADTH health technology assessment — project protocol).

ISSN: 1927-0127 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
FACT-G	Functional Assessment of Cancer Therapy: General
GRIPP2	Guidance for Reporting Involvement of Patients and the Public (version 2)
HTA	Health Technology Assessment
ICTRP	International Clinical Trials Registry Platform
LSR	living systematic review
MA	meta-analysis
MDASI-LC	MD Anderson Symptom Inventory for Lung Cancer
MeSH	Medical Subject Headings
MOOSE	Meta-analyses Of Observational Studies in Epidemiology
NMA	network meta-analysis
OS	overall survival
PFS	progression-free survival
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
SABR	stereotactic ablative radiotherapy
SBRT	stereotactic body radiation therapy
SR	systematic review
SRS	stereotactic radiosurgery

Introduction and Rationale

Cancer and Oligometastatic State

Cancer is the leading cause of death in Canada, comprising 30% of all death events.[1] In 2019, an estimated 220,400 new cancer cases and 82,000 deaths occurred.[1] Tumour metastasis is the main cause of cancer-related death.[2-4] The development of metastases is a potential complication among patients with cancer.[5] Metastasis occurs when cancer cells, originating from one part of the body, moves from the place of origin (primary tumour) and spreads to another location to form one or more tumours.[5,6] The extent of systemic disease and the number, size, and location(s) of lesions can affect the overall prognosis of a patient.[7]

In 1995, Hellman and Weichselbaum first introduced the term oligometastatic state, which acknowledges that the process of cancer metastasis occurs along a continuum — from localized to widespread metastatic disease.[8,9] Oligometastases may represent a paradigm shift in the treatment intent for metastatic cancer: a limited number of metastases can be resected or ablated, and the treatment outcome may be curative.[10] Hellman and Weichselbaum (1995) described two 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 agents, 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." Moreover, as these two classes of oligometastases represent different clinical scenarios, they are associated with different prognoses and also may require different treatments.[11] Since the publication of this seminal paper by Hellman and Weichselbaum, the concept of oligometastasis has been well accepted but specific criteria that define an oligometastatic state, such as the number of metastases and organ sites, are still unclear.[11,12] 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.[13] Imaging is currently the most relevant diagnostic method for defining oligometastatic cancer, which is broadly understood as limited metastatic lesions.[11,14]

Stereotactic Ablative Radiotherapy

Treatment options for patients presenting with oligometastatic cancer may include, but are not limited to, surgery or stereotactic ablative radiotherapy (SABR).[15] Though 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 local control.[15] 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.[16-18] First developed in Sweden in the early 1990s,[19] SABR builds on the treatment delivery paradigm used to treat brain tumours with intracranial stereotactic radiosurgery (SRS) but it targets tumours outside of the brain (e.g., lungs, liver, bone, and lymph nodes).[16] SABR relies on an imaging component to map the treatment area using CT scans or MRI, tumour motion reduction and reproducible patient setup strategies (e.g., respiratory compression, body immobilization devices [e.g., alpha-cradle/vacuum-lock system]), and advanced radiotherapy delivery techniques using conventional linear accelerators or novel precision delivery systems.[16] 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, and MR-Linac.[20] SABR is considered an alternative to surgical resection and is often the preferred option for patients with cancer who are 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 at high risk for post-operative complications.[11]

SABR in Canada

The availability of SABR has increased across Canada.[21] In 2014, a survey of 41 Canadian radiotherapy centres reported that five provinces (British Columbia, Alberta, Manitoba, Ontario, Quebec) had centres with SABR capacity, though substantial growth was expected. Currently, all provinces in Canada have SABR capability.[22] SABR is also available in some northern centres (e.g., Northeast Cancer Centre in Ontario).[23] Canadian centres that are using SABR treat primary tumours and oligometastases in different areas of the body, such as the lungs, liver, bone, and lymph nodes.[21,24]

CADTH received input received 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, the 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 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 as compared to 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 the jurisdictions that responded expressed an interest in an economic analysis of the expanded use of this technology.

Thus, 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.[25] In the summer of 2016, the National Health Service (UK) produced a policy document stating that they would not routinely commission SABR for oligometastatic cancer given that there was insufficient evidence to support the provision of treatment.[26] However, recent evidence identified has suggested the potential for improved health outcomes with the use of SABR oligometastases, such as overall survival (OS) and progression-free survival (PFS).[27,28] A Health Technology Assessment (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 and jurisdictional feedback, and results of the detailed scoping exercise, the HTA will address the following policy questions:

- Should SABR be used for the treatment of patients with oligometastatic cancer?
  - If yes, what are the appropriate patient selection criteria and treatment-related characteristics (e.g., dose, treatment site)?
  - If yes, what are the main considerations to guide the appropriate implementation of SABR in Canada?

Objective

The purpose of this HTA is to address the decision problem by first assessing the clinical benefits and harms of SABR in the treatment of patients with oligometastatic cancer. Considerations regarding the appropriate implementation of SABR will also be identified. As the HTA review progresses, other considerations such as stakeholder perspectives and ethical issues may be assessed. An analytical framework guiding the clinical review can be found in Appendix 1.

Deliverables

The following deliverable(s) are planned:

- A systematic review (SR) of the clinical evidence
- An Environmental Scan of current implementation status, practice, barriers, and facilitators to implementing SABR

The clinical evidence regarding SABR is still developing; therefore, a staged approach to this HTA will be followed. There are several ongoing clinical trials. CADTH will first conduct a clinical SR and Environmental Scan. If the initial results of the clinical SR suggest the use of SABR for the treatment of oligometastatic cancer, further analyses may be conducted. For example, a review of the ethical considerations in relation to the use of SABR or an exploration of patients, caregivers, and clinicians' experiences with or perspectives on the use of the technology.

As noted above, 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 of 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.

This protocol document provides research questions and methods for a clinical SR. If other analyses emerge as relevant, a priori detailed methods will be appended and provided as an amendment to this protocol.

Research Questions

The clinical review will address the decision problem by answering the following research questions. Details on the specific interventions and outcomes for the clinical research question are included in Table 1.

Clinical Review

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

Methods

This is a multi-phase HTA. The current focus of the protocol is the clinical SR portion of the HTA. This protocol was written a priori in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[29] guideline for clarity, transparency, and completeness. The protocol has been prospectively registered in the international repository, PROSPERO, and any deviations from the protocol will be disclosed in the final report. Updates to the PROSPERO submission will be made accordingly (PROSPERO registration submitted; registration number not yet received).

Clinical Review

Scoping

The protocol for the clinical review was informed by a CADTH Rapid Response Report,[30] an informal scoping review of the existing literature, discussion with clinical experts, and patient engagement.

The Rapid Response Report was conducted in February 2019 (search range: January 1, 2014 to January 8, 2019) to obtain an understanding of the clinical effectiveness and cost-effectiveness of SABR for patients with oligometastatic cancer.[30] Details on the complete methodology for the published Rapid Response Report are available in the publication.[30] Based on the eligibility criteria of the report, clinical evidence of limited quality from three retrospective cohort studies conducted outside of Canada was identified. These studies suggested that the use of SABR, compared to other treatment options (e.g., metastasectomy, radiotherapy), may not improve OS rates for patients with oligometastatic cancer. Since there is no standard definition for oligometastatic cancer,[11,31] the report relied on the authors of the included studies to explicitly state that they included patients with oligometastatic cancer.

To further aid the detailed scoping process, a supplementary literature search was conducted using the same inclusion criteria as the Rapid Response Report, but the search range was expanded (inception through July 2019). Additional clinical studies were identified, including one randomized controlled trial (RCT) comparing SABR to standard of care palliative treatment in patients with oligometastatic cancers[24] and one meta-analysis (MA) that synthesized 28 studies examining SABR for oligometastatic renal cell carcinoma.[32] The RCT included patients from four countries, including patients from Canada.[24] Additional details about the detailed scoping process are provided in the Scoping Brief.[33] Together, the Rapid Response Report and supplementary literature search identified five studies (one SR with an MA, one RCT, three retrospective cohort studies) regarding the clinical effectiveness of SABR for oligometastatic cancer and more than 10 additional, potentially relevant studies depending on the criteria used to define oligometastatic cancer (e.g., studies describing a population with limited metastatic lesions versus explicitly stating oligometastatic cancer). Despite this, there were no HTAs and there was a lack of SRs identified for this topic area.

The SR with an MA identified (of unknown quality) focused on oligometastatic renal cell carcinoma, which does not synthesize results related to other oligometastatic cancer sites, and it is also unclear how SABR could be best utilized based on certain factors (e.g., number of metastases, location of metastases).

After discussion with clinical experts in the field of oligometastatic cancer, CADTH decided to expand on the population selection criteria for this HTA, by allowing for inclusion of studies that used terminology such as *oligo*, *limited*, or *few* to describe limited numbers of metastases. The effects of applying different thresholds as the maximum number of metastases will be examined through a subgroup analysis, if possible. For the purposes of this review, oligometastatic cancer includes patients with limited metastatic lesions at any time during the course of a patient's disease (i.e., at presentation, prior to initial therapy, after initial therapy, relapse) without a previous history of widespread metastatic disease.[11,34-37] Studies of patients with a history of widespread metastatic disease (i.e., patients with induced oligometastatic cancer) will 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 (i.e., "patients with tumours early in the chain of progression with metastases limited in number and location"[8]).[11]

CADTH engaged one adult patient who had cancer and a lived experience of SABR for their oligometastatic cancer. Once consent was obtained, the patient discussed, through an interview, their health condition, treatment experiences, and perspectives on those experiences. The patient interview was used to raise ideas and inform the review protocol, including eligibility criteria; the PICO elements from the research question in the protocol (population, intervention, comparison, and outcomes) were shared and discussed. Additionally, key concepts identified by the assessment team through prior scoping activities were explored; for example, the advantages and the challenges to undergoing SABR. This discussion highlighted the importance of health-related quality of life outcomes, especially pain during and after treatment, the ability to return to work, and to be active. In particular, the patient emphasized that OS and PFS were the most important of the protocol's listed outcomes. They also reported that lesional control was a shared goal with the patient and their oncologist. This information supplemented the decision-making process for the protocol's eligibility criteria.

Study Design

This clinical review will be designed as a living systematic review (LSR) to answer research questions 1 and 2, enabling continual surveillance and updates to the analysis contingent on following a priori stopping rules (see Continual Surveillance Through an LSR subsection for more details). The LSR model will allow for ongoing assessment of the clinical effectiveness and safety of SABR, incorporating 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 any other relevant trials or studies that may be currently under way.

This review will comprehensively explore the clinical effectiveness and safety of SABR for oligometastatic cancer for a number of different cancers and any metastatic sites amenable to SABR, as outlined in research questions 1 and 2. Specifically, CADTH will conduct an LSR in consideration of methods outlined in the Cochrane Collaboration's guidance[38] and the Cochrane Handbook.[39] As defined by that guidance, an LSR is an SR that is underpinned by continual, active monitoring of the evidence, and incorporates relevant new evidence in a timely manner as it becomes available.[40] An LSR is justified in this circumstance as the three main criteria[38] to warrant this type of review are fulfilled:

- the review is a priority for decision-making, as evidenced by survey results, jurisdictional input, and the topic being prioritized as a CADTH HTA
- there is an important level of uncertainty in the existing clinical evidence, as described by the National Health Service,[26] the recent Rapid Response with Critical Appraisal,[30] and the paucity of HTAs and SRs on this topic area
- there is emerging evidence,[30] with more than 60 ongoing studies in various types of oligometastatic cancer,[25] that will impact the conclusions of the LSR.

LSRs follow the same core methods and review steps as a standard SR. Thus, standard SR methods (e.g., screening, data extraction, and risk of bias assessment) will be followed to conduct the baseline review. The clinical review will transition into the living mode once the baseline review is published. The LSR design will enable continual surveillance of new clinical research evidence ensuring the review findings remain current and reflect the incoming results from clinical trials. Details regarding updating and ending the LSR can be found below under the Continual Surveillance Through an LSR subsection.

Literature Search Methods

The literature search for clinical studies for the baseline review will be performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[41] The complete search strategy is presented in Appendix 2.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be SABR and oligometastatic cancer. Clinical trial registries will be searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters will be applied to limit the retrieval by study type. Retrieval will be limited by publication dates after January 1, 1990. Conference abstracts will be excluded from the search results, though they will be reviewed by a clinical team member for forecasting purposes.

The initial search will be completed in spring 2020. After the initial literature search is completed, monthly alerts will be conducted until the end of the stakeholder feedback period, at which time alerts will run every three months to support the LSR phase of the HTA. The clinical trial registries search will be updated before the completion of the stakeholder feedback period, and then switch to updates every six months.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist,[42] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, SR repositories, patient-related groups, and professional associations. Google will be used to search for additional internet-based materials. The grey literature search will be updated before the completion of the stakeholder feedback period. See Appendix 2 for more information on the grey literature search strategy. Grey literature will be updated every six months for the baseline review, as well as the LSR phase of the HTA.

Additional literature search methods related to updating the LSR are found in the Continual Surveillance Through an LSR section.

Eligibility Criteria

The review's eligibility criteria, including the specific population, intervention, comparators, outcomes (PICO) for the clinical research questions can be found in Table 1. The inclusion criteria were informed by the CADTH Rapid Response Report,[30] the informal scoping review of the existing literature, patient engagement, and consultation with clinical experts.

Table 1: Eligibility Criteria for Clinical Research Questions

Population
Include: 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. Exclude: patients with metastases only in the brain, and patients with a previous history of widespread metastatic disease
Intervention(s)
SABR of any dose or fractionation alone or in combination with one or more concurrent or neoadjuvant therapies, for example: • 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: • 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
Q1: Outcomes restricted to the following: • OS[a,b] • PFS[a,c] • freedom from progression[d] • health-related quality of life[a,e] • lesional control[f] • systemic therapy use (e.g., yes/no; number of cycles of chemotherapy and/or systemic therapy; total duration of chemotherapy and/or systemic therapy) **Q2:** Outcomes restricted to the following: • adverse events (as described in CTCAE version 5.0[43])

Study Design(s)
Include: Comparative study designs, including: • randomized controlled trials • non-randomized controlled trials[g] • cohort studies[h] • case-control studies Exclude: • 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

CTCAE = Common Terminology Criteria for Adverse Events; 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 by an interview conducted by CADTH.

[b] OS: time from randomization [or diagnosis for non-RCTs] 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 non-RCTs] to any documented progression of disease at any site using Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[44] 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 non-RCTs] to any documented progression of disease at any site using RECIST criteria, [44] 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 will be considered; possible questionnaires include: Functional Assessment of Cancer Therapy: General [FACT-G], European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30], MD Anderson Symptom Inventory - Lung Cancer Module [MDASI-LC]).

[f] Lesional control: time of randomization [or diagnosis for non-RCTs] until radiological evidence of progression at the treated site or development of a previously unknown metastatic lesion and be measured on a lesion based on analysis using RECIST criteria.[44]

[g] Non-randomized 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.[45]

[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.[46] Only study designs providing comparative evidence are eligible for inclusion.

[i] SABR was first developed in the early 1990s in Sweden[19] and the term oligometastatic state was first introduced by Hellman and Weichselbaum in 1995.[8] Given this, only studies published after the year 1990 will be included, which should include a complete list of relevant studies.

For this HTA, the population of interest is patients with oligometastatic cancer. Acknowledging that the definition for oligometastatic cancer is still evolving,[11] CADTH elected to not use number of metastatic lesions as a limit in the eligibility criteria; the number of metastatic lesions will be considered as a subgroup analysis. The population eligible for this HTA includes patients with oligometastatic cancer, described by study authors as having limited metastatic lesions using terminology such as *oligo*, *limited*, or *few*. Studies which do

not include such descriptions of the patient population that present them as having oligometastatic cancer will be excluded. Oligometastasis includes situations where the primary tumour is present, not present (i.e., removed), treated, or untreated.[13] Thus, the status of the primary tumour will not be a part of the eligibility criteria since a participant can have oligometastases regardless of the state of the primary tumour.[13] This review will include 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 and/or systemic treatment) that shows interval growth (or regrowth) with or without a systemic-free internal.[11,34-37] Details of the oligometastatic patient population, including any descriptions regarding the clinical situation of the diagnosis (e.g., limited metastases at presentation, before initial therapy, after initial therapy, relapse) and status of the primary tumour, will be extracted from included studies when available.

Studies with mixed populations of patients who do not meet the review inclusion criteria will be included if the results pertaining to the subgroup who do meet inclusion criteria are reported separately. If results for the population of interest are not reported separately, studies with a mixed study population will be included if at least 80% of the population meets the inclusion criteria. However, studies will be excluded when this criterion is not met (i.e., less than 80% meeting the inclusion criteria or unable to judge due to missing data).

The intervention of interest is SABR (synonym: SBRT, with or without one or more concurrent or neoadjuvant therapies). Stereotactic radiosurgery aimed to target only brain metastases will be excluded since ablative therapy to the central nervous system is more clinically established and not the focal area of interest for this HTA.[47] For instances where the intervention is SABR in combination with one or more concurrent or neoadjuvant therapies, the study will be eligible for inclusion if the comparator also includes the same concurrent or neoadjuvant therapies in order to explore the true effects (benefits, harms) of SABR.

For the clinical effectiveness outcomes for research question 1, data at all time points will be of interest and included. With this in mind, different time points will not be combined (e.g., five-year OS data will be analyzed and combined with other five-year OS data). In cases where studies use more than one tool to assess health-related quality of life, all data will be included. For the safety outcomes for research question 2, data that allow for comparisons between the intervention and comparator groups will be of interest and included (e.g., frequencies or prevalence of individual or grades of adverse events [e.g., grades 1-2 versus grades 3-5] reported for each group are in scope, but non-quantifiable lists of adverse events for both groups are not in scope).

The review will be limited to studies published in English, which is supported by evidence that suggests excluding non-English publications from evidence synthesis does not change conclusions.[48,49]

Exclusion Criteria

Studies will be excluded if they do not meet the selection criteria outlined in Table 1 or if they are duplicate publications. If there are multiple publications fulfilling the inclusion criteria from the same study (i.e., same population), they will all be included if presenting unique results (e.g., different outcomes or time points), and data will be extracted and discussed as

one single study. Studies of patients with a history of widespread metastatic disease (i.e., patients with induced oligometastatic cancer) will 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.[11] Studies that include patients with a history of metastases without reporting enough detail to determine whether this represents a history of oligometastasis (i.e., limited or few metastases) versus a history of widespread metastatic disease will also be excluded.

A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Study Selection

To address the clinical effectiveness and safety of SABR for the treatment of oligometastatic cancer, primary studies that evaluated clinical effectiveness or safety and reported results related to clinical effectiveness or safety outcomes will be considered for inclusion. Two reviewers will use the SR management software DistillerSR (Evidence Partners, Ottawa, Canada) to facilitate independent title and abstract screening, as well as full-text study selection.

Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search (i.e., academic database and grey literature searches), as well as any articles identified by content experts.

Full texts articles that are judged to be potentially relevant by at least one reviewer will be retrieved and independently assessed for possible inclusion based on the pre-determined selection outlined in Table 1 (i.e., if one reviewer believes the citation should be screened at the full-text level, it will move forward to the next level of screening; no conflict resolution will be performed). Two reviewers will independently screen full-text publications, compare their included and excluded studies from the full-text review, and resolve any disagreements through discussion until consensus is reached; a third reviewer will be involved for adjudication, if required. A list of included studies will be posted for stakeholder review for 10 business days, and feedback and any additional studies identified for potential inclusion will be reviewed following the above process.

Studies identified via monthly database search alerts and semi-annual grey literature search alerts meeting the selection criteria of the review will be incorporated into the analysis if they are identified before the end of the stakeholder feedback period of the baseline review. After the stakeholder feedback period, database search alerts will be scheduled to occur quarterly, and grey literature search alerts will continue to occur semi-annually, as part of the LSR protocol. Any studies identified after the stakeholder feedback period will be retained and later screened for the second iteration of the review (i.e., first update of the LSR process).

The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[50] flow chart.

Data Extraction

Reviewers will use Microsoft Excel and the SR management software DistillerSR[51] to facilitate data extraction. A data extraction form will be developed within DistillerSR[51] to document and tabulate all relevant information from included studies. Relevant information includes both descriptive data and results reported in all included studies; the form may be

updated during the data extraction phase to reflect additional details reported by the included studies that are relevant to the outcomes of interest.

Data from each included study will be extracted by one reviewer and checked for accuracy by a second reviewer. Disagreements will be resolved through discussion until consensus is reached, involving a third reviewer if necessary. If data related to OS, PFS, and adverse events (i.e., the outcomes identified as most important by the interviewed patient and clinical experts consulted) are missing from or conflicting in the included studies, attempts will be made to contact the corresponding authors to clarify or obtain missing information. Relevant OS, PFS, or adverse events data will be deemed missing if numerical data supporting qualitative statements or findings presented in figures are absent, and authors will be contacted if those data are needed for an MA. Relevant OS, PFS, or adverse events data will be deemed conflicting if there are discrepancies within the study (e.g., between the abstract and the main text of a publication) or between different publications of the same study, and authors will be contacted. If no response is received from study authors to a request for clarification of discrepant data reporting by the end of the stakeholder feedback period for the baseline review, all results will be reported in the HTA; for numerical data, the most conservative value will be used for conflicting data, if needed (e.g., in an MA). If no response is received from study authors to a request for numerical data related to findings presented in a figure, the best numerical estimate based on the figure will be used, if needed. From the included studies, data will be extracted based on following levels:

- Study level: description of publication (e.g., first author last name, title, publication year, journal), study characteristics (e.g., clinical trial registry identification number, trial acronym, objectives, study design, year of study conduct, sample size, study setting, country of study conduct, study funding source).
- Patient level: number of patients, age (mean, standard deviation), proportion of women or female patients, 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., present versus removed, 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/treatment), equipment type (brand).
- Comparator level: type (e.g., surgery, conventional radiotherapy, chemotherapy, immunotherapy, hormone therapy, other ablative treatment [cryoablation, radiofrequency ablation, etc.], 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.
- 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 will be 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 for survival outcomes), any results of statistical tests reported on those measures, and whether fixed-effects or random-effects models were used will be extracted.

Critical Appraisal

Quality Assessment of Individual Studies

The risk of bias for included studies will be systematically evaluated using the methods described in the Cochrane Risk of Bias assessment tool 2 for RCTs (RoB 2)[52] and the Risk of Bias for Nonrandomized Studies (RoBANS)[53] for non-randomized studies, including cohort and case-control studies. The RoB 2 tool[52] allows for the assessment of five 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 will be answered with a yes, probably yes, probably no, no, or no information. For each item, a judgment of low risk of bias, high risk of bias, or some concerns will be assigned, with rationale for each decision included in the comments box field.[52] Based on judgments across the five domains, an overall risk of bias will be assigned to each study (low, high, or some concerns).[52] The RoBANS tool[53] also allows for the assessment of risk of bias across eight domains (the possibility of the target group comparisons, target group selection, confounder, exposure measurement, blinding of assessors, outcome assessment, incomplete outcome data, selective outcome reporting). For each item, a judgment of low, high, or unclear will be assigned with rationale for each decision included in the comments box field. The risk of bias assessments of the included studies will be performed by one reviewer and verified by a second reviewer. Disagreements will be resolved through discussion, involving a third reviewer if necessary. The tools will be used as a guide to evaluate the risk of bias in the included studies, and additional insight beyond the items on the instruments will be provided, when applicable. Summary scores will not be calculated; rather, the strengths and limitations of each included study and how they affect the study findings will be described narratively. Results of the quality assessment will not be used to exclude studies from this review.

Data Analysis and Synthesis

Narrative Synthesis

Narrative syntheses will be performed, including the presentation of study characteristics (e.g., the total number of studies included, PICO elements, study designs, publication years, and countries in which the studies were conducted) and findings within the main text and summary tables. This review will synthesize all findings based on the condition, oligometastatic cancer; cancer types within oligometastatic cancer will be analyzed separately as subgroups of interest as specified below. The direction and size of any observed effects and any results of statistical tests reported on those effects will be 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). The following subgroups will be examined narratively and quantitatively, as appropriate (see MA of Primary Clinical Effectiveness Studies subsection):

Clinical research question 1 subgroups:

- age, sex, and gender
- location of primary tumour site
- number of metastases sites (e.g., single versus multiple sites)
- number of metastases (e.g., ≤ 3, ≤ 5, > 5)

- location of metastases (e.g., metastatic site-specific [bone only, lung only, liver only, etc.], with versus without brain metastases)
- previous treatment of primary tumour (e.g., yes, no)
- previous treatment of metastases (e.g., yes, no).

A narrative summary of the results of the methodological assessments for each included study will be provided. Specifically, tables will be 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.

MA of Primary Clinical Effectiveness Studies

For OS, PFS, and adverse events (i.e., the outcomes identified as most important by the interviewed patient and clinical experts consulted), the results of the included studies will be pooled, using random-effects MAs, if data are sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. Clinical and methodological heterogeneity will be assessed in consultation with clinical experts and will consider patient and study design factors that might be expected to affect the clinical effectiveness and/or safety of SABR. When possible, separate MAs will be conducted for each OS, PFS and harms outcomes and between randomized and non-randomized studies; results from randomized and non-randomized studies will not be pooled.

When deemed appropriate, dichotomous data will be pooled using odds ratios or risk ratios, continuous data using mean differences or standardized mean differences (if different instruments were used to measure the same construct), and survival data using hazard ratios, all with corresponding 95% confidence intervals (CIs). If adjusted effects measures are reported, the adjusted results will be used in the primary analysis, and differences between unadjusted and adjusted results will be discussed. If required measures of variance are not available, variances will be imputed where possible. If non-parametric data (e.g., medians or quartiles) are reported, parametric data (e.g., means and standard deviations) will be estimated using the methods from Wan and colleagues.[54] Forest plots will be created for individual summary estimates. MAs will be carried out using the Cochrane Review Manager software (version 5.3, or the most up-to-date version available at the time of analysis).

Unit of Analysis

As aggregate data will be used, the unit of analysis will be the study.

Heterogeneity and Subgroup or Meta-Regression Analysis

Statistical heterogeneity will be assessed using graphical presentations (e.g., forest plots) and calculations of Cochran's chi-square test and the I^2 statistic, which quantifies the variability in the effect estimates due to heterogeneity rather than chance (i.e., sampling error). Heterogeneity will be interpreted with the guidance from Higgins and colleagues,[55] which assigns adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively. Heterogeneity will be interpreted with true P values. The same subgroups described in the narrative synthesis section will be considered for MA as well, provided each subgroup meets the assumptions required for conducting an MA.

Publication Bias

If there are 10 or more included studies of a given study design and a particular outcome, publication bias will be assessed visually using funnel plots and objectively using Egger's regression test and Begg's rank correlation test.[56]

Reporting of Findings

The SR will be prepared in consideration of relevant reporting guidelines (e.g., PRISMA statement,[57] PRISMA harms,[58] Meta-analysis Of Observational Studies in Epidemiology [MOOSE] reporting checklist,[59] and Synthesis Without Meta-analysis (SWiM) guideline[60]) and will meet the criteria outlined in A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist.[61]

Patient Engagement

CADTH involves patients, 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 a Framework for Patient Engagement in HTA. The framework includes Standards for Patient Involvement in Individual HTAs and is used to support and guide our activities involving patients. For this HTA, the value of relevance and the belief that patients have knowledge, perspectives, and experiences that are unique and contribute to essential evidence for HTA will guide our patient engagement activities. To date, CADTH has engaged one adult cancer patient with a lived experience of SABR for their oligometastatic cancer. CADTH may engage with more patients as the project progresses.

Invitation to Participate and Consent

A potential participant was identified through radiation oncologists with experience of SABR, and through the Canadian Partnership Against Cancer. 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 HTA, the purpose of engagement and the nature of engagement activities. The Patient Engagement Officer obtained the person's informed consent.

Engagement Activities

Patients will be asked to reflect on their own personal experiences at several time points during assessment including:

- prior to clinical protocol finalization (completed; described in the Clinical Review
- Scoping section)
- during drafting of the initial SR
- upon completion of final clinical report.

Patient perspectives gained through engagement processes will be used in several ways, including ensuring relevance of outcomes of interest for the clinical assessment and commenting on other key concepts that were initially identified through prior scoping activities. The involvement of patients may also prompt the research team to consider the possible need to explore avenues of analysis that may have been missed or underdeveloped, and possibly add additional concepts. The involvement of patients will also enable the research team to consider the evidence alongside an understanding of the wider

experiences of patients and caregivers. Patients will provide valuable feedback on the clarity of writing, and comment on the relevance of the findings to Canadian patients and families.

Once preliminary findings of the initial SR are available, the participant will be invited to be interviewed. The conversation will explore the participant's perceptions of key findings, including if the findings are understandable, and if they reflect personal experiences or understandings. This conversation will be used to consider the possible need to explore avenues of analysis that have been missed or underdeveloped, add additional concepts or experiences that relate to identified categories, or inform the processes underlying SABR treatment and the context of analysis.

Final conversations will be had with the participant upon completion of the final clinical report. Through conversation, CADTH will share the key results of the full assessment and describe how engagement activities were used.

Reporting

The reporting of this section will follow the GRIPP2 Short Form reporting checklist,[62] and include the outcomes, discussion and reflection items as suggested by that guidance to outline in a final report the process of engagement and where and how participants' contributions were used in the assessment. The Patient Engagement Officer will keep track of patient engagement activities and interactions in detailed notes and communications. CADTH will provide reflections and critical perspectives on the experience of the involvement for the patient and the research team in the final report.

Continual Surveillance Through an LSR: Updating and Transition Out of Living Mode

At the end of stakeholder feedback, the review will be activated into living mode with an update scheduled every three months.

Literature Search Methods

To support the LSR phase of the HTA, the Research Information Specialist will switch the frequency of running academic database alerts from every month to every three months once the stakeholder feedback period for the baseline review has closed. In addition, the frequency of running clinical trial registry alerts will change from every month to every six months. Grey literature searches will continue to be updated every six months. The same databases and grey literature sources will be searched for the LSR as the baseline review.

Eligibility Criteria

The inclusion and exclusion criteria will be identical to the criteria of the baseline review.

Study Selection

The Research Information Specialist will send any new citations from academic databases on a quarterly basis and grey literature on a semi-annual basis for two clinical team members to independently screen (title and abstracts, followed by full texts) using the same processes and software (i.e., DistillerSR) as the baseline review. Thus, every three months, academic databases search results will be screened and every six months both academic database and grey literature search results will be screened.

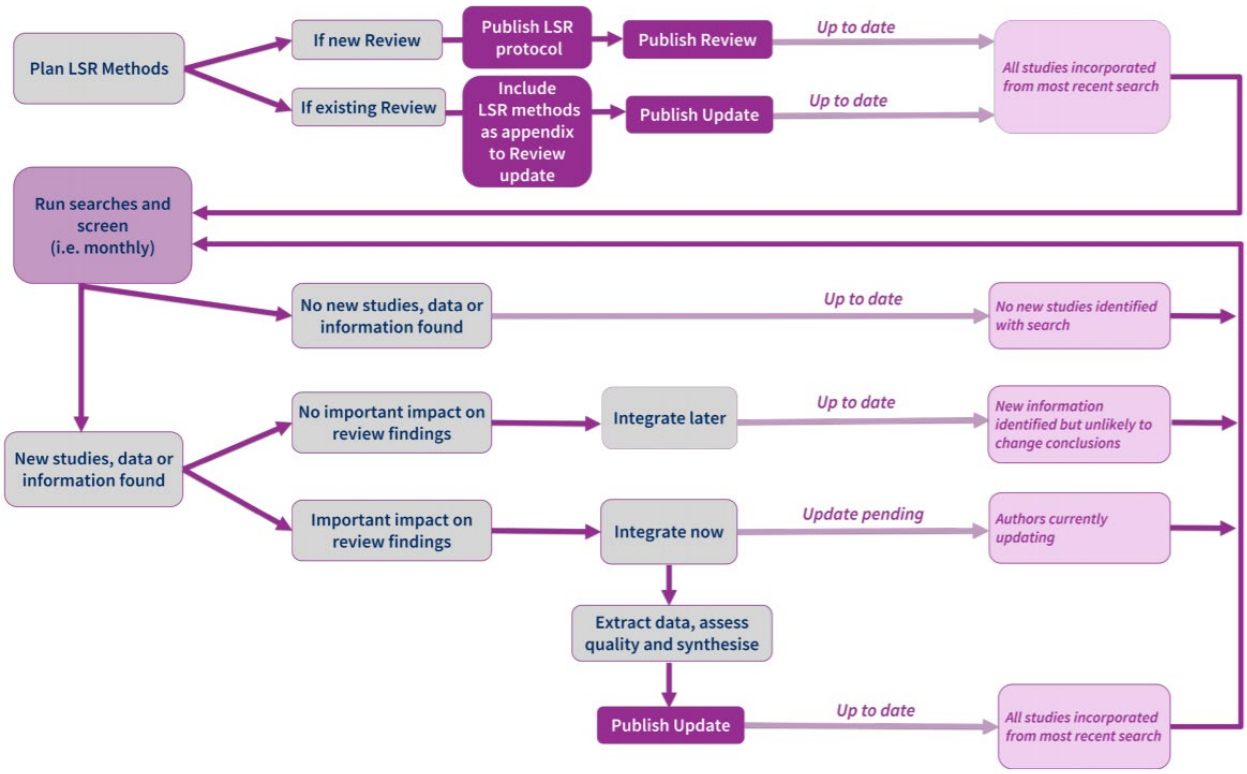
As illustrated in Figure 1, at the time of an update:

- If the ongoing searches have identified no new relevant evidence, the status of the review will remain up-to-date, no data extraction will be needed, and rationale will remain as *no new relevant studies identified in search*, needing no update to the evidence of the review.
- If the ongoing searches have identified new relevant evidence that is unlikely to change the review conclusions, the status of the review will remain up-to-date, with the rationale being *new information identified but unlikely to change conclusions* needing no update to the evidence of the review at this time.
- If the ongoing searches have identified new relevant evidence that is likely to change the review conclusions, a review update will be conducted to integrate all new relevant evidence up to that point.

The following signals at the outcome level (i.e., OS, PFS, adverse event outcomes), for the main as well as subgroup analyses, will be considered relevant evidence that is likely to change the review conclusions and therefore will prompt a review update:

- Quantitative signals (if an MA is conducted in the baseline review or during a previous update): change in the direction of the findings (e.g., from minus to plus); change in the statistical significance of an effect estimate using a conventional threshold (e.g., from the 95% CI crossing 0 or 1 to no longer crossing); or a relative change of ≥ 50% in the magnitude of an effect estimate.[63]
- Qualitative signals (if only a narrative synthesis is conducted in the baseline review or during previous update): a qualitatively different characterization of effectiveness that affects clinical decision-making (e.g., a new harm, a new alternative therapy, expansion of treatment to a new patient subgroup).[63] In the event a new relevant study is identified that enables a new MA to be conducted in addition to a narrative synthesis, the MA will be conducted if resources are available.
- Quantitative or qualitative signals (if no findings have been found in the baseline review or during a previous update): any new relevant findings that can be synthesized narratively or using MAs as per the methods outlined above.

Figure 1: The Cochrane LSR Workflow with Publication Outputs



Note. The Cochrane Figure[38] described running searches and screening on a monthly basis. For this LSR, CADTH will be running academic databases on a quarterly basis and grey literature on a semi-annual basis. Every three months, academic databases search results will be screened and every six months both academic database and grey literature search results will be screened.

Data Extraction

Data extraction will involve the same processes as the baseline review. Data extraction will be triggered in instances where full-text screening of articles has identified new evidence that is likely to change the review conclusions (i.e., when a review update is prompted based on a quantitative or qualitative signal outlined above). However, data will be extracted from all relevant studies that had been identified up to that point (i.e., including relevant studies that had been identified but deemed unlikely to change the review conclusions and did not trigger an update to the evidence of the review).

Critical Appraisal

Critical Appraisal will involve the same processes as the baseline review and will be conducted when updating the review.

Data Analysis and Synthesis

Narrative Synthesis. When a study is identified that triggers an update to the evidence of the review, the narrative synthesis of the data will involve the same processes as the baseline review, including the incorporation of new findings into the study characteristics and findings within the main text and summary tables. The direction and size of any observed effects will

be updated and 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). A narrative summary of the results of the methodological assessments for each new included study will be provided, and the conclusions at the outcome level will be updated, as needed.

Meta-Analysis. The decision to conduct MAs as well as the processes for re-running MAs will be the same as the baseline review. Per the Cochrane Collaboration's guidance,[38] CADTH will not control for the type I error rate due to frequent updating.

Periodic Review of LSR and Transitioning Out of LSR Mode

After the LSR has been in living mode for 12 months, the clinical review team will review the appropriateness of continuing to maintain the review in living mode on an annual basis. Considering Cochrane's guidance,[38] the review will be continually updated as described until the review questions no longer meet all three criteria for the reasons to conduct an LSR:

- the research question is no longer a priority for decision-making
- a reasonable level of certainty has been reached in the existing evidence
- research that might impact the conclusions of the review is no longer emerging (e.g., the research area is no longer active).

CADTH will consider the research questions no longer being a priority for decision-making in situations where the intervention has been superseded or withdrawn. 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. This may be assessed by asking the jurisdictional representatives whether there have already been decisions made about SABR and whether additional information from a clinical SR would change their current practices. The LSR may also transition out of LSR mode based on lack of available resources.

Opportunities for Stakeholder Feedback

All stakeholders (health care professionals, patients, drug manufacturers, associations, and other interested parties) will be given the opportunity to provide feedback on the draft included studies list and the draft report for the clinical SR. Unpublished data identified as part of the feedback process may only be included if the source of data is in the public domain.

Protocol Amendments

If amendments are required at any time during the review, reasons for changes will be recorded in a study file and subsequently reported within the final report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data, according to the amendments.

Protocol amendments may also be completed to provide detailed methods for additional analyses (e.g., review of ethical considerations) deemed relevant after consideration of preliminary clinical results, the Environmental Scan, and ongoing Canadian economic analyses. Updates to the PROSPERO submission will be made accordingly (PROSPERO registration submitted; registration number not yet received).

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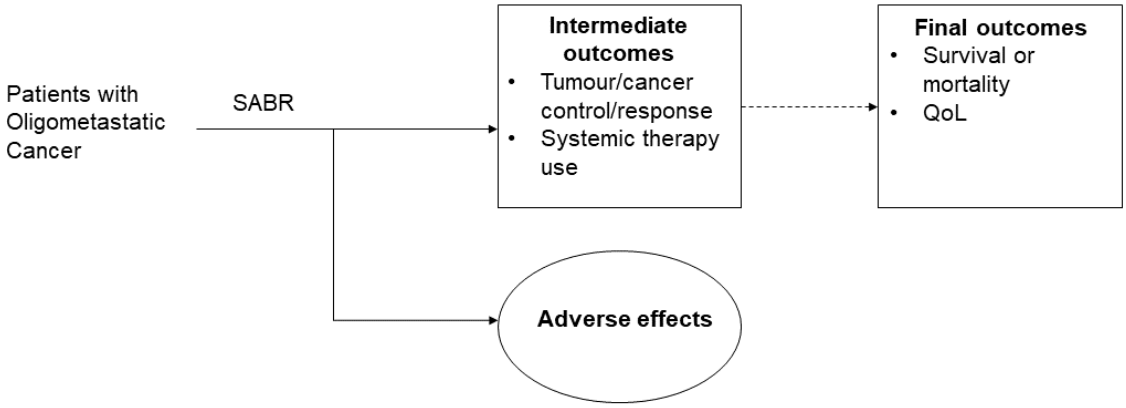
Appendix 1: Analytic Framework



SABR = stereotactic ablative radiotherapy; QoL = quality of life.

Appendix 2: Literature Search Strategy

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:	November 26, 2019
Alerts:	Monthly search updates until project completion. After completion search alerts will occur every three 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 modulat* 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 modulat*) 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 tacic RT* or stereotacic 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 oligoprogress* or oligorecur* or oligopersist* or oligofraction* or oligoclonal* or oligosynchron*).ti,ab,kf,kw.
15	(oligo* adj5 (meta* or progress* or recur* or persist* 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 modulat* 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.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
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 modulat*) 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.
32	(SRS* or SABR* or SBRT* or mdSBRT* or FSR or FSRT or LINAC* or DCA or VMAT or IMRS or IMPT or stereo tacic RT* or stereotacic RT* or stereo taxic RT* or stereotaxic RT* or systemSBRT*).ti,ab,kw,dq.
33	(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,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 oligoprogress* or oligorecur* or oligopersist* or oligofraction* or oligoclonal* or oligosynchron*).ti,ab,kw,dq.
39	(oligo* adj5 (meta* or progress* or recur* or persist* 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]	

CLINICAL TRIAL REGISTRIES		
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. 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:	To be completed
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.