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CADTH SCOPING BRIEF

Stereotactic Ablative Body Radiotherapy for the Treatment of Oligometastatic Cancer

CADTH

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Cite As: *Stereotactic Ablative Body Radiotherapy for the Treatment of Oligometastatic Cancer.* Ottawa: CADTH; 2020 Feb. (CADTH scoping brief).

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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Current Considerations

Stereotactic ablative body radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), is a novel form of radiation treatment that delivers high precision doses to specific body sites over a shorter treatment period than conventional radiotherapy.[1] Treatment with SABR involves an imaging component to map the treatment area, and a radiotherapy component to deliver the treatment. It is an alternative to surgical treatment and an option for non-surgical candidates as it does not require recovery before resuming systemic therapy, and can be used to treat sites that are not surgically accessible.[2]

The availability of SABR has increased across Canada[3] and there is interest in expanding its use to new indications such as oligometastatic disease. Oligometastatic cancer occurs when the disease has metastasized to a limited number of sites (usually five or fewer) and is not rapidly spreading to other sites.[4] It may represent a paradigm shift for metastatic cancer – if oligometastatic sites can be resected or ablated, there is the potential that it is curable.[4]

The use of SABR for the ablation of oligometastases is an active area of research with more than 50 ongoing studies in various types of oligometastatic cancer.[5] In the summer of 2016, the National Health Service (UK) produced a policy document stating that they would not routinely commission SABR for oligometastatic disease given that there was insufficient evidence to support the provision of treatment.[6] However, recent evidence has suggested the potential for improved overall and progression-free survival with the use of SABR for ablation of oligometastases.[7,8]

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, more provinces (including New Brunswick, Saskatchewan, and Nova Scotia) report SABR availability.[3,9] SABR is available in some northern centres (e.g., Northeast Cancer Centre in Ontario).[10] Currently, the Canadian centres that are using SABR treat oligometastases in different areas of the body. These areas include the lungs, liver, bones, prostate, and lymph nodes.

Input received from Canadian jurisdictions identified a several common considerations regarding the use and implementation of SABR. There is a desire to determine the standard of care 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, treatment sites, immobilization methods, tracking, and image guidance). Decision-makers are also seeking more information regarding the long-term outcomes of treatment with SABR. In addition to patient treatment and disease management, the jurisdictions expressed interest in information regarding the implementation of the technology including how other jurisdictions have successfully operationalized the use of technology (e.g., billing codes, time to treatment, length of individual treatment sessions, staffing). All the jurisdictions that responded expressed an interest in an economic analysis of the technology.

Decision Problem

Feedback from within the jurisdictions suggests that decision-makers are concerned with a several practice and policy issues related to SABR use. These include:

- Should clinical indications for the use of SABR be expanded to include oligometastatic cancer?

- What definition for oligometastatic disease should be used to determine which patients receive the treatment?
- Should funding be allocated, and should capital procurement of technology be pursued to support expanded use?
- What resources and infrastructure are required to support the successful implementation and provision of the technology?
- What additional technical infrastructure, training, and resources are required to support the provision of SABR for oligometastatic cancer in Canada?
- Given that equipment and expertise may be primarily found in urban centres, what measures are required to ensure equitable access to SABR?
- What commitments to data monitoring, research, and reporting should sites using SABR be required to make?

Based on the context and jurisdictional feedback, the purpose of a CADTH review of this topic would be to inform the following:

- 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 and enablers to the implementation of SABR in Canada?

Proposed Products

Based on the detailed scoping process and jurisdictional feedback, the suggested approach for this topic is:

- A systematic review of the clinical evidence
- An Environmental Scan of current implementation status and practice uses, as well as barriers and facilitators to implementing SABR
- Patient engagement to help contribute to understanding patients' and caregivers' perspectives and experiences
- Input into or review of the reports by an ethicist with experience in advanced cancer.

The evidence regarding SABR is still developing; therefore, a staged approach is recommended. If the clinical, and Environmental Scan results indicate the need for further work regarding a full ethics review or further need for additional consideration of patients' and caregivers' experiences, additional products, and/or reassessments will be considered. Canadian economic analyses are currently under way to assess the value for money and affordability of SABR in Canada. No additional economic analyses from CADTH will be conducted at this time.

Methods for Information Gathering

Scoping Briefs are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided as a summary of important, current assessment information on this topic to inform CADTH work and have not been externally peer reviewed. More detail regarding methods is available in Appendix 1.

The Technology

Treatment options for patients presenting with oligometastatic cancer may include, but are not limited to, surgery or SABR.[11] Though surgery (i.e., surgical resection) is considered the gold standard for the treatment of certain oligometastases (e.g., hepatic, colorectal), SABR may be a non-invasive alternative to achieve local control.[11] SABR is a non-invasive cancer irradiation method. It builds on the concepts that inform intracranial stereotactic radiosurgery (SRS) but targets tumours outside of the central nervous system.[1]

SABR was first developed in Sweden in the early 1990s.[12] It is a type of external radiation therapy and the method of delivery enables precise delivery of higher doses of radiation, as compared with traditional radiotherapy, to specific sites using hypofractionated dose schedules (a few large fractions over a short overall treatment time).[1] This precision helps spare normal tissue.[13,14] The technique relies on image guidance (usually X-ray or CT scans and more recently MRI) and motion reduction strategies (e.g., compression, body frame or immobilization devices [e.g., alpha-cradle/vacuum-lock system]).[1] SABR can be delivered using conventional linear accelerators or novel precision delivery systems. 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.[15]

Who Might Benefit?

The term oligometastatic state acknowledges that the process of cancer metastasis occurs along a continuum — from locally confined cancers to widespread metastatic disease.[16,17] Oligometastatic state is believed to be curable in select patients.[16,18] The concept of oligometastasis has been well accepted but the specific criteria of what defines an oligometastatic state, such as what is considered *metastases limited number,* is still an ongoing process.[19] A current definition of oligometastasis is “a type of metastasis in which cancer cells from the original (primary) tumour travel through the body and form a small number of new tumours (metastatic tumours) in one or two other parts of the body.”[13] However, other factors may also play an important role in establishing criteria for an oligometastatic state such as volume, histology, genetics, and location of tumour(s).[19]

The primary population that SABR use will impact are individuals diagnosed with oligometastatic cancer. Patients may be further grouped based on the number of metastases (e.g., one to three versus four or more) and or the location of the primary cancer site. The most common method used to stratify patients with oligometastatic disease for treatment is by the total number of metastatic sites.[20] Patients may also be further grouped by size of metastases; dose; fractionation; number of visits; duration of treatment; equipment type; and position or immobilization method.

Clinical Considerations

A summary with critical appraisal was conducted in February 2019 (search range: January 1, 2014 to January 8, 2019) to obtain an understanding of the clinical effectiveness of SABR for patients with oligometastatic cancer.[21] Based on the eligibility criteria of the report, clinical evidence of limited quality from three retrospective cohort studies conducted outside of Canada were identified. These studies suggested that the use of SABR, compared with other treatment options (e.g., metastasectomy, radiotherapy), may not improve overall survival rates for patients with oligometastatic cancer. Since there is no standard definition for oligometastatic disease, the report relied on the authors of the included studies to explicitly state that they included patients with oligometastatic cancer. It is likely that some citations that fit within one of the definitions of oligometastatic cancer were excluded because interpretation of oligometastatic cancer was beyond the scope of the report. In addition, there were two clinical practice guidelines and six ongoing clinical trials identified in the report, and the findings from this literature may provide additional insight on SABR for oligometastatic cancer now and as it becomes available.

To further aid the detailed scoping process, a supplementary literature search was conducted (search range: inception through July 2019). Additional clinical studies were identified, including one randomized controlled trial (RCT) comparing SABR with standard of care palliative treatment in patients with oligometastatic cancers[9] and one meta-analysis that synthesized 28 studies examining SABR for oligometastatic renal cell carcinoma.[22] The RCT included patients from four countries, including patients from Canada.[9] Together, the Rapid Response Report and supplementary literature search identified five studies (one meta-analysis, 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 disease.

From a clinical effectiveness perspective, there is an opportunity for CADTH to contribute to the understanding of how SABR may help patients with oligometastatic cancer by conducting a living systematic review. There were no health technology assessments and a lack of systematic reviews identified for this topic area, the meta-analysis (of unknown quality) identified focuses on oligometastatic renal cell carcinoma, which does not synthesize other oligometastatic cancer sites (e.g., lungs, prostate) and it is also unclear how SABR could be best utilized based on population type, number of metastatic sites, dose, and other factors. A full systematic review with the involvement of clinical experts would help discern an appropriate definition for oligometastatic cancer that is inclusive of patients in Canada who would be eligible for the treatment if SABR is recommended for use and reimbursement within Canada. Continual surveillance of new clinical research evidence in the form of a living review would ensure the review findings remain current and reflect the incoming results from clinical trials. Moreover, this review will draw from the additional considerations above and ensure the review is relevant for the Canadian health care system.

Cost and Economic Considerations

The current cost of the intervention in Canada is unclear based on our literature search.

One economic evaluation was identified during scoping that addressed the cost-effectiveness of SABR in a Canadian context.[23] This economic evaluation assessed the cost-effectiveness of SABR compared with radiotherapy, surgery, and best supportive care in Canadian patients with stage I non-small cell lung cancer from the Canadian public health care payer perspective with a 10-year time horizon.[23] SABR was found to be cost-effective for inoperable and borderline-inoperable patients, while lobectomy was the most cost-effective option in operable patients. No other oligometastatic diseases were considered.

Two non-Canadian economic evaluations were identified. In one cost-utility study comparing SABR with video-assisted thoracoscopic surgery wedge resection and systemic therapy in five different patient cohorts, stratified by cancer type in an American setting, the cost-effectiveness of SABR depended on the cancer type.[24] In the other study, the target population was unclear and, as such, it is challenging to interpret its results.[25]

CADTH contacted a Canadian research group who are currently assessing the cost-effectiveness and affordability of SABR. Their economic evaluation and budget impact analysis could be used to address the questions on the potential cost-effectiveness and affordability of SABR in Canada.

Perspectives and Experiences

An initial scoping search did not retrieve any qualitative literature on the topics of oligometastatic cancer or SABR. One qualitative study with two publications[26,27] was identified that investigated the communication and decision-making experiences of 10 patients who underwent SABR or surgery for early-stage non-small cell lung cancer. The findings highlighted the importance of the therapeutic alliance and patient-centred care when treating patients with lung cancer.

As SABR is a newer treatment modality and oligometastatic cancer is an emergent clinical paradigm, it is likely that qualitative research has not yet been undertaken or published on this topic. Analogous concepts include radiation therapy and metastatic or advanced cancer; however, initial searches on the concepts of radiation therapy and metastatic cancer did not yield any primary qualitative studies or syntheses specific to this topic. Studies and syntheses of types of cancer (e.g., breast, lung) may contain information on patients' decision-making for treatment and experiences of and coping strategies with treatment related side effects for radiation therapy. Because of substantial differences between the use of SABR for oligometastatic cancer (i.e., that the treatment is in a curative paradigm), issues of transferability in patient populations (e.g., advanced, non-curable cancer versus potentially curable cancer) and technology (e.g., duration and dose of treatment) would be a substantial challenge in a qualitative review.

Given the patient population, the highly specialized and multidisciplinary nature of the therapy, the integral use of advanced imaging, and the emerging evidence base for SABR for oligometastatic cancer, several domains of experiences and perspectives may be informative for CADTH's assessment. The specialized and centralized nature of the therapy and its location in urban centres in Canada[3] suggests that travel may form part of patients'

and their caregivers' experience, even as the therapy can be delivered in a shorter number of treatment sessions (and potentially reduce travel for patients and their caregivers).[10,28]

Additionally, consideration of harms and benefits of the treatment, particularly in the context of an emerging evidence base, point to the importance of patient-provider relationships and informed consent process, particularly where long-term harms and benefits may not be well-established. Patient experiences of radiation therapy may provide insight on the long-term harms and side effects of cancer treatment and point to other services and supports that help patients' cope with side effect and maximize potential improvements in quality of life. Specifically, the emotional, social, and psychological dimensions of advanced cancer, including those experienced during diagnosis, treatments, and survivorship may inform how SABR is implemented and delivered. There is an opportunity for CADTH to contribute to understanding how patients' and caregivers' experience SABR for oligometastatic cancer through patient engagement, which could draw about the patient and caregiver considerations and would ensure the relevance of this review for patients.

Equity and Ethical Considerations

An initial scoping search did not retrieve any articles describing analyses of ethical considerations for the use of SABR for people living with oligometastatic cancer. A targeted Google search for ethical issues related to SABR and oligometastatic cancer helped to identify common framings of, and common promises and concerns around SABR, and SABR for oligometastatic cancer.

Of note, the use of SABR for oligometastatic disease represents a shift in treatment potential from palliative to curative. With this shift comes discussions of hope, which are accompanied by hype due to the potential for long-term curative therapy. At the same time, however, uncertainty regarding the clinical benefits and harms of SABR in this patient population raises notions of unrealistic expectations from patients and presents an immediate challenge to health care decision-makers who might not have the required information to help patients make a fully informed choice. Given the complex nature of the technology, its delivery, and the high doses of radiation, patients who do experience harms following SABR may experience disproportionately greater harms than those typical of more standard radiotherapy.

Further, expanded use of SABR would require a shift in resource allocation; meaning, if SABR is used in this population other treatments might not be available for people living with other conditions. Although resource allocation decisions are inherently value-based, in the context of clinical uncertainty they are particularly challenging. If long-term evidence generation suggests that the hope for increased patient benefit does not materialize, implementing disinvestment strategies will be challenging in the Canadian context given available treatment alternatives.

There is the additional potential to further exacerbate existing equity considerations in access to cancer treatments depending on the place of residence (e.g., between urban, rural, and remote locations), and income status.[29]

It is apparent that an ethical lens will need to be brought to considerations of expanding the use of SABR to include the treatment of people living with oligometastatic cancer. It is unclear, however, whether the concerns identified through the scoping process are comprehensive, or the most salient, for this context. Input from an ethicist with experience in advanced cancer and treatment innovation is warranted.

Implementation Considerations

The use of SABR may represent a change to the way provinces and territories administer care for patients with oligometastatic cancer. There are several factors that would need to be considered when making such a change.

SABR is a technically complex treatment delivery technique that requires a multidisciplinary team approach[30] including a radiation oncologist, radiation therapist, a physicist, and radiation oncology nurses.[31] The SABR procedure is time and labour intensive requiring both economic and staff resources. Cancer centres may not be adequately prepared with the necessary experience and technical expertise (both personnel and facility-wise) required for delivery of care. SABR requires additional treatment planning time[32] (which is different compared with other forms of radiotherapy treatment),[31] various specialized patient positioning, stabilization, and immobilization equipment options that vary depending on the target site,[31] respiratory coaching methods, and service commissioning.[30] Additionally, the use of SABR puts new demands on the time available for the equipment to be used for other procedures and the question arises about how to operationally accommodate a growing number of indications for complex treatments.

There is no current consensus to determine which patients with oligometastatic cancer should be chosen to receive SABR.[33] Processing delays may occur between the clinical decision to use SABR for treatment and the actual delivery of treatment to the patient and is a challenge that may impact care and potentially patient outcomes depending on how long their treatment is delayed.

Currently, there is variation between jurisdictions in both the availability of SABR and the oligometastatic sites that are being treated. This variation in availability was identified in 2014[3] and continues to be present based on consultations with jurisdictional contacts. There is interest specifically in how Canadian jurisdictions are using the technologies, what the standard of care in Canada is, how jurisdictions with large populations are incorporating SABR into their daily operations, and how both staff and financial resources are allocated. Information regarding the methods that have been used to successfully plan and staff existing centres could be useful for the other jurisdictions when they consider how to establish SABR in their centres.

No literature was identified that specifically examined issues related to the implementation of SABR for oligometastatic cancer.

CADTH could contribute by providing information regarding barriers and facilitators to the implementation of SABR, such as:

- Training and management of staff resources
- Options for the optimization or standardization of SABR workflow
- Information regarding existing methods used to prioritize which patients, or which oligometastatic sites, would benefit most from SABR
- Identify resources that support the successful implementation of SABR.

Manufacturer Information

Device	Year Health Canada licence acquired	Manufacturer
LINAC		
XKnife	1999	Integra Lifesciences
Versa	2014	Elekta
Infinity	2010	
Precise	2014	
TrueBeam	2010	Varian Medical Systems
Novalis Tx	2014	
Trilogy	2009	
Clinac	2002	
Accuray Tomotherapy	2010	Accuray
Radixact	2017	
Precision Delivery Systems		
CyberKnife	2009	Accuray
Synergy	2014	Elekta
Gamma Knife Icon	2009	
ExacTrac	2017	Brainlab

Summary of Key Considerations

The scoping process revealed several key considerations regarding the proposed review of SABR for oligometastatic cancer. Based on these considerations, general directions for conducting the review are proposed.

The main considerations identified are:

- The proposed review was requested by a CADTH customer. A total of five jurisdictions have expressed interest in the review. In their feedback, the jurisdictions identified several common considerations regarding the use and implementation of SABR such as patient selection and management, long-term outcomes of treatment with SABR, operationalization of the technology, and the economic implications.
- There is currently a limited body of evidence available on the clinical effectiveness of SABR for oligometastatic cancer. A previously published CADTH rapid review and a supplementary literature search identified five studies regarding clinical effectiveness and more than 10 additional, potentially relevant studies. Given the jurisdictional interest in clinical outcomes and considering the existing evidence and expected publication of findings from ongoing trials, CADTH is proposing to conduct a living systematic review of the clinical evidence. This review may be helpful to address uncertainty around the clinical effectiveness of SABR in treatment of oligometastatic cancer.
- The scoping process identified one relevant economic evaluation conducted in the Canadian context and two non-Canadian economic studies that together offer limited evidence on the economic impact of SABR. Furthermore, an economic evaluation and budget impact analysis of SABR for oligometastatic cancer is currently being conducted in a Canadian jurisdiction by a research group in British Columbia. CADTH will monitor

ongoing Canadian economic analyses and assess whether their scopes are relevant and if results are available to other interested Canadian jurisdictions.

- The initial scoping search indicates that there is a lack of qualitative literature on the topic of oligometastatic cancer or SABR and the analogous concepts of radiation therapy and metastatic cancer. Given the paucity of evidence, it is unlikely that a CADTH qualitative review will yield a comprehensive and helpful analysis on the use of SABR for oligometastatic cancer. However, there is an opportunity for CADTH to contribute to understanding how patients and caregivers experience SABR for oligometastatic cancer through patient engagement.
- Similarly, the scoping search did not identify any literature on ethical considerations related to the use of SABR for oligometastatic cancer. Nonetheless, some common ethics themes may apply to this topic, such as the potential challenge for patients to make an informed choice regarding the treatment and the potential impact of SABR implementation on equity in access to cancer treatments. Overall, the existing evidence base may not allow for a CADTH review of ethical considerations, but such a review may be warranted in the future as more evidence on SABR for oligometastatic cancer becomes available.
- No literature specific to implementation issues associated with SABR for oligometastatic cancer was retrieved through the initial scoping search. However, as noted, the jurisdictions have expressed broad interest in a review of implementation considerations. A CADTH Environmental Scan of Canadian and international facilities that provide SABR treatment for oligometastatic cancer may help address the information needs of the jurisdictions in this regard.

To our knowledge, this is the first Health Technology Assessment proposed to explore SABR for oligometastatic cancer.

	Current proposed PICO
Population	Patients, of any age, with oligometastatic cancer (sites may include prostate, liver, lung, head and neck, kidney, colon, breast, and bone) Subgroups: • number of metastases (e.g., 1 to 3 versus 4 to 5) • size of metastases • primary tumour sites • dose, fractionation, number of visits, and duration of treatment • equipment type • position and immobilization of patient
Intervention	SABR alone or in combination • chemotherapy (e.g., nivolumab) Exclude: stereotactic radiosurgery
Comparator(s)	Usual care, other cancer treatments (e.g., chemotherapy, surgery, radiotherapies), no treatment, SABR at a different dose than intervention arm
Outcomes	Clinical effectiveness (e.g., local control, pain control, tissue sparing, progression-free survival, overall survival, quality of life), safety (e.g., toxicity [acute, late]) Implementation status, implementation barriers and facilitators

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Appendix 1: Methods

Limited iterative literature searches were conducted by an information specialist on key resources including MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were SABR and metastatic cancer. Where possible, retrieval was limited to the human population. The search is up to date as of August 28, 2019.