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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Stereotactic Body Radiotherapy for Oligometastatic Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	February 6, 2019
Report Length:	23 Pages

CADTH

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Cite As: Stereotactic Body Radiotherapy for Oligometastatic Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottawa (ON): CADTH; 2019 Feb. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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

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Abbreviations

EGFRm	epidermal growth factor receptor mutated
ICER	incremental cost-effectiveness ratio
NSCLC	non-small cell lung cancer
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
RTRT	real-time tumor-tracking radiotherapy
VATS	video-assisted thoracic surgery

Context and Policy Issues

Cancer is the leading cause of death in Canada, comprising 30% of all death events.[1] In 2017, an estimated 206,200 new cancer cases and 80,800 deaths occurred.[1] The development of metastases is a potential, and sometimes frequent, complication among patients with localized cancer.[2] Metastases occurs when cancer cells originating from one part of the body moves from the place of origin (primary tumor) and spreads to another location to form one or more tumors.[2,3] The extent of systemic disease and the number, size, and location(s) of lesions can affect the overall prognosis of a patient.[4]

In 1995, Hellman and Weichselbaum first introduced the term oligometastatic state, which acknowledges that the process of cancer metastasis occurs along a continuum – from locally confined cancers to widespread metastatic disease.[5,6] Oligometastatic state is believed to be curative in select patients.[5,7] Since the publication of this seminal paper, the concept of oligometastasis has been well accepted but the specific criteria of what defines oligometastatic state, such as what is considered 'metastases limited number', is still an ongoing process.[8] Currently, the National Cancer Institute, part of the National Institutes of Health, defines oligometastasis as "a type of metastasis in which cancer cells from the original (primary) tumor travel through the body and form a small number of new tumors (metastatic tumors) in one or two other parts of the body."[9] However, other factors may also play an important role in establishing criteria for oligometastatic state such as volume, histology, genetics and location of tumor(s).[8]

Nevertheless, treatment options for patients presenting with oligometastatic cancer may include, but are not limited to, surgery or stereotactic body radiotherapy.[10] Though surgery (i.e., surgical resection) is considered the gold standard for the treatment of certain oligometastases (e.g., hepatic, colorectal), stereotactic body radiotherapy may be a non-invasive alternative to achieve local control.[10] Stereotactic body radiotherapy, also known as stereotactic ablative radiotherapy, is a type of external radiation therapy that helps spare normal tissue by precisely delivering radiation to tumors in the body (except the brain); the total dose of radiation is divided into smaller doses given over several days.[9,11] Ultimately, the feasibility of stereotactic body radiotherapy as a standard of care will depend on its clinical and cost-effectiveness compared to other cancer treatments. Thus, this report aims to summarize the evidence regarding the clinical effectiveness and cost-effectiveness of stereotactic body (ablative) radiotherapy for patients with oligometastatic cancer.

Research Questions

1. What is the clinical effectiveness of stereotactic body (or stereotactic ablative) radiotherapy for the treatment of oligometastatic cancer?

2. What is the cost effectiveness of stereotactic body (or stereotactic ablative) radiotherapy for the treatment of oligometastatic cancer?

Key Findings

Clinical evidence of limited quality from three retrospective cohort studies involving patients with oligometastatic cancer suggest that the use of stereotactic body (ablative) radiotherapy may not improve overall survival rates compared to other cancer treatments. No evidence of a difference was found between stereotactic ablative radiotherapy and other cancer treatments for progression-free survival, freedom from failure of local strategy or freedom from local progression. One study found real-time tumor-tracking radiotherapy was significantly more effective than stereotactic body radiotherapy for local control of adrenal metastasis in patients with oligometastasis, but the stereotactic body radiotherapy patients had fewer adverse events (zero versus four events).

One relevant cost-effectiveness study was identified on the use of stereotactic body radiotherapy for patients with oligometastatic cancer. This study found that stereotactic body radiotherapy and video-assisted thoracic surgery wedge resection may be cost-effective in select patients with pulmonary oligometastases; effectiveness of either treatment option depended on histology, efficacy, and tolerability of the treatment as well as patient preferences.

Given the limited availability and low quality evidence, the effectiveness and use of stereotactic ablative radiotherapy for oligometastatic cancer remains uncertain.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, PubMed (for non-Medline records), the Cochrane Library, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 8, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with oligometastatic cancer
Intervention	Stereotactic body radiotherapy (or stereotactic ablative radiotherapy)
Comparator	Usual care, other cancer treatments (e.g., chemotherapy, surgery, radiotherapies)
Outcomes	Q1: Clinical effectiveness, safety

	Q2: Cost effectiveness outcomes (e.g., quality-adjusted life years)
Study Designs	Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies Q2: Economic evaluations

Exclusion Criteria

Citations were excluded if they: (i) did not meet the selection criteria outlined in Table 1; (ii) were duplicate publications; or (iii) were published prior to 2014. Studies that did not directly describe the target population as patients with oligometastatic cancer were excluded; studies that included a patient population that may fall within the definition(s) of oligometastatic cancer, but were not explicitly stated, are listed in Appendix 5.

Critical Appraisal of Individual Studies

The included clinical studies were critically appraised using Downs and Black checklist[12] and the economic study was assessed using the Drummond Checklist.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 798 citations were identified in the literature search. Following screening of titles and abstracts, 720 citations were excluded and 78 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 75 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised three non-randomized (retrospective cohort) studies and one economic evaluation. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Three retrospective, comparative cohort studies of clinical effectiveness were identified.[15-17] The cohort studies consisted of two single-centre studies[16,17] and one two-centre study.[15]

One economic evaluation was identified.[18] This cost-effectiveness study used a cycle length of one-month and a five-year analytic time horizon from a societal perspective. The authors used a Markov model and set the societal willingness to pay as $100,000 per quality-adjusted life years (QALYs) gained. To inform their analysis, they derived the model parameters from several (>30) referenced sources.[18]

Country of Origin

The body of evidence originated from four countries: Japan,[15] Italy,[17] the Netherlands,[16] and the United States.[18]

Patient Population

All non-randomized studies examined adult populations (18+ years old) diagnosed with oligometastatic cancer that underwent stereotactic body (ablative) radiotherapy or usual care.[15-17] Specifically, patients had pulmonary (lung) oligometastases[16,17] or adrenal metastatic tumors.[15] Each patient group had a median age of ≥ 61 years, and the median follow-up for patients was ≥17.5 months.[15-17] The sample size varied between studies, ranging from 20 to 170 patients. There were no restrictions on sex or gender reported. Included clinical studies did not report on whether patients were community-dwelling, residing in assisted living, convalescent, long-term or palliative care. All clinical studies provided basic demographic characteristics of their included participants.[15-17]

The economic evaluation assessed the cost-effectiveness of three initial management strategies, including stereotactic body radiotherapy, for pulmonary oligometastases in patients with melanoma, non-small cell lung cancer (NSCLC; three types), and colon cancer.[18] The model included five hypothetical cohorts with patients with one to five pulmonary oligometastases, and was estimated with a state transition Markov model. The patients entered into the model corresponded to the average diagnosis of the cancer: 65 years for melanoma and 70 years for NSCLC and colon cancer.[18]

Interventions and Comparators

One study compared stereotactic ablative radiotherapy to pulmonary metastasectomy[16] and one study compared stereotactic body radiotherapy to lung metastasectomy.[17] In addition, the other clinical study compared general-stereotactic body radiotherapy to real-time tumor-tracking radiotherapy (RTRT).[15] This study provided dosage and frequency information; the RTRT group received 48 Gy in 5-8 fractions over two weeks and the general-stereotactic body radiotherapy group received 40-50 Gy in 5-8 fractions over two weeks or 60-70 Gy in 10 fractions over two weeks.[15]

For the economic evaluation, the study compared stereotactic body radiotherapy to video assisted thoracic surgery wedge resection and systemic therapy; all treatments were considered initial therapeutic options.[18]

Outcomes

The clinical studies investigated and reported on the following outcomes: overall survival,[15-17] progression free survival,[16,17] adverse events,[15] local (tumor) control,[15] freedom from failure of local strategy,[16] and freedom from local progression.[16]

The primary endpoints for the economic evaluation were QALYS and cumulative costs.[18] When there was no dominant strategy, incremental cost-effectiveness ratios were calculated.[18]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Clinical Studies

The three retrospective cohort studies clearly reported their objectives, interventions, comparators, main outcomes, characteristics of the study population, and main findings.[15-17] All studies appear to have used appropriate statistical tests to assess the main outcomes.[15-17] One study did not provide estimates of random variability when presenting findings.[15] Two studies reported that the patient groups being compared came from the same centre.[16,17] In contrast, one study had the patients of the control group come from one centre and the patients of the intervention group came from two different centres.[15] Thus, selection bias may be present for this study, especially since the authors did not provide context for why this was the case. Moreover, it is unclear whether the participants from all three studies were representative of the source population (i.e., external validity), and whether the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receives.[15-17] When interpreting the internal validity of the study, one important factor to consider is blinding. In this case, blinding of patients or the investigators responsible for analyzing the study was not described. [15-17] If blinding was not performed in any capacity, the authors could have included this as a limitation in the discussion for improved transparency. In addition, median length of follow-up was different between groups in one study[17] and it is not clear if the median length of follow-up was the same between groups for the other two studies.[15,16] Acknowledging that total length of follow-up can vary between groups given to the nature of the patient population (i.e., patients diagnosed with cancer), the authors could have provided more details about the intended length of follow-up for both groups as well as the median follow-up for both groups. Moreover, the included studies did not describe sample size calculations to determine statistical power.[15-17] Funding and declaration of potential conflicts of interest were described in one study,[15] but was not reported for the other two included clinical studies.[16,17]

Economic Evaluation

The included economic evaluation[18] satisfied the majority of the criteria outlined in the Drummond checklist.[13] For example, the economic evaluation described the viewpoint of the analysis, rationale for choosing the interventions, time horizon, form of the economic evaluation, and rationale for their approach in relation to the question addressed. The evaluation also described the sources of effectiveness and the primary outcome measure of the analysis.[18] However, it is unclear if the findings from this economic evaluation could be applied to the Canadian population since the cost of cancer treatments (i.e., stereotactic body radiotherapy, video assisted thoracic surgery wedge resection, systemic therapy) may vary between countries.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Stereotactic Body (Ablative) Radiotherapy versus Usual Care

Overall survival rates

None of the three studies found a significant difference in overall survival rates when comparing stereotactic body (ablative) radiotherapy to other cancer treatments (i.e., g-stereotactic body radiotherapy versus RTRT,[15] stereotactic ablative radiotherapy versus

pulmonary metastasectomy,[16] stereotactic body radiotherapy versus lung metastasectomy).[17]

Progression-free survival

One cohort study did not find a significant difference in progression-free survival between stereotactic ablative radiotherapy and pulmonary metastasectomy groups.[16] Another cohort study was not able to determine differences between stereotactic body radiotherapy and lung metastasectomy because different follow-up protocols were applied to the two cohorts.[17]

Local control rates

One cohort study found that RTRT was significantly more effective than stereotactic body radiotherapy for local control of adrenal metastasis.[15]

Adverse events

In one cohort study, Grade 2 acute reactions (i.e., appetite loss, nausea, vomiting) were described in four patients from the RTRT group.[15] No acute reactions for Grades 3 to 5 or late adverse reactions for Grade 2 to 5 were reported for either RTRT or stereotactic body radiotherapy groups.[15]

Freedom from failure of local strategy

One study investigated freedom from failure of local strategy and found no differences between stereotactic ablative radiotherapy and pulmonary metastasectomy treatments.[16]

Freedom from local progression

One study investigated freedom from local progression and found no differences between stereotactic ablative radiotherapy and pulmonary metastasectomy treatments.[16]

Cost-Effectiveness of Stereotactic Body (Ablative) Radiotherapy versus Usual Care

The economic evaluation estimated the cost-effectiveness of three initial management treatments for pulmonary oligometastases, including stereotactic body radiotherapy, video-assisted thoracic surgery (VATS) wedge resection, and systemic therapy.[18] The investigation considered five different cohorts of patient disease: melanoma; NSCLC adenocarcinoma, NSCLC squamous cell carcinoma, NSCLC epidermal growth factor receptor mutated (EGFRm) adenocarcinoma, and colon cancer. In brief, "*VATS wedge resection or stereotactic body radiation therapy can be cost-effective in select patients with pulmonary oligometastases, depending on histology, efficacy, and tolerability of treatment and patient preferences*."[18]

For melanoma and NSCLC adenocarcinoma, the base case model suggested stereotactic body radiotherapy was the most cost-effective strategy when considering expected cost per net QALYs compared to VATS wedge resection and systemic treatments. For melanoma, systemic treatment (i.e., pembrolizumab) improved QALYs, but had a higher cost that was not cost-effective. Sensitivity analyses for both melanoma and NSCLC adenocarcinoma revealed the variable with the greatest influence in the model was the patient utility status of the stereotactic body radiotherapy group after treatment.[18]

For NSCLC EGFRm adenocarcinoma, systemic therapy (i.e., erlotinib) was the most cost effective in the base case compared with stereotactic body radiotherapy and VATS wedge resection. Sensitivity analyses revealed the variables with the greatest influence in the

model were progression-free survival and toxicity of the systemic therapy group and patient utility of both the stereotactic body radiotherapy and systemic therapy groups. Stereotactic body radiotherapy was marginally cost-effective compared to systemic therapy when calculating the incremental cost-effectiveness ratio (ICER), assuming a willingness-to-pay of $100,000 per QALY.[18]

In the base case, systemic therapy (i.e., paclitaxel/carboplatin) was the most cost-effective for NSCLC squamous cell carcinoma compared to stereotactic body radiotherapy and VATS wedge resection. Stereotactic body radiotherapy had an improvement in QALY but was not cost-effective relative to the systemic treatments. Sensitivity analyses revealed the variables with the greatest influence in the model were cost of stereotactic body radiotherapy and patient utility status of the systemic therapy group.[18]

For colon cancer, VATS wedge resection was the most cost-effective for colon cancer in the base case compared to stereotactic body radiotherapy and systemic treatments. Sensitivity analyses revealed the variable with the greatest influence in the model was the patient utility status of the VATS wedge resection group after treatment.[18]

Limitations

There are certain limitations to consider when reviewing the report.

The included clinical studies are retrospective cohort studies[15-17] and no systematic reviews or randomized controlled trials met the eligibility criteria. Without eligible randomized trials, it is difficult to be certain of the true effects of stereotactic body (ablative) radiotherapy for patients diagnosed with oligometastatic cancer. Moreover, there is currently no standardized definition of oligometastatic state;[8] therefore, this report relied on study authors to explicitly state that they included patients with oligometastatic cancer. It is possible that some citations were excluded that fit within one of the definitions of oligometastatic cancer but were excluded because interpretation of oligometastatic cancer was beyond the scope of this report.

One economic evaluation met the eligibility criteria and was included in this report.[18] Although this cost-effectiveness study was considered high quality, we cannot draw definitive conclusions about the cost-effectiveness of stereotactic body (ablative) radiotherapy from one study alone. Moreover, the findings from this study are only relevant to the types of cancer included in this evaluation.

None of the included studies of this report were conducted in Canada. Therefore, it is unclear how generalizable the results of these studies are to the Canadian population or to the Canadian healthcare system.

Conclusions and Implications for Decision or Policy Making

Three non-randomized, clinical studies were included from the search. These studies suggest that the use of stereotactic body (ablative) radiotherapy, compared to other treatment options, may not improve overall survival rates for patients with oligometastatic cancer. One cohort study found local control for adrenal metastasis in patients with oligometastasis was most effective with RTRT versus stereotactic body radiotherapy; no significant differences were found for the other outcomes investigated by the three cohort studies. To reduce uncertainty of the clinical effectiveness of stereotactic body (ablative) radiotherapy, additional studies using rigorous methods, such as high-quality randomized

trials with sufficient sample sizes, are required. Moreover, specific criteria to define oligometastatic state are required to aid future knowledge syntheses.

One relevant cost-effectiveness study was identified and concluded that stereotactic body radiotherapy and VATS wedge resection may be cost-effective in certain patients with pulmonary oligometastasis, depending on histology, efficacy, and tolerability of the treatment and patient preferences.

The limited amount of high-quality evidence indicates that additional clinical and cost-effectiveness studies comparing stereotactic body (ablative) radiotherapy to other cancer treatments are required to determine its place in the care pathway for patients with oligometastatic cancer.

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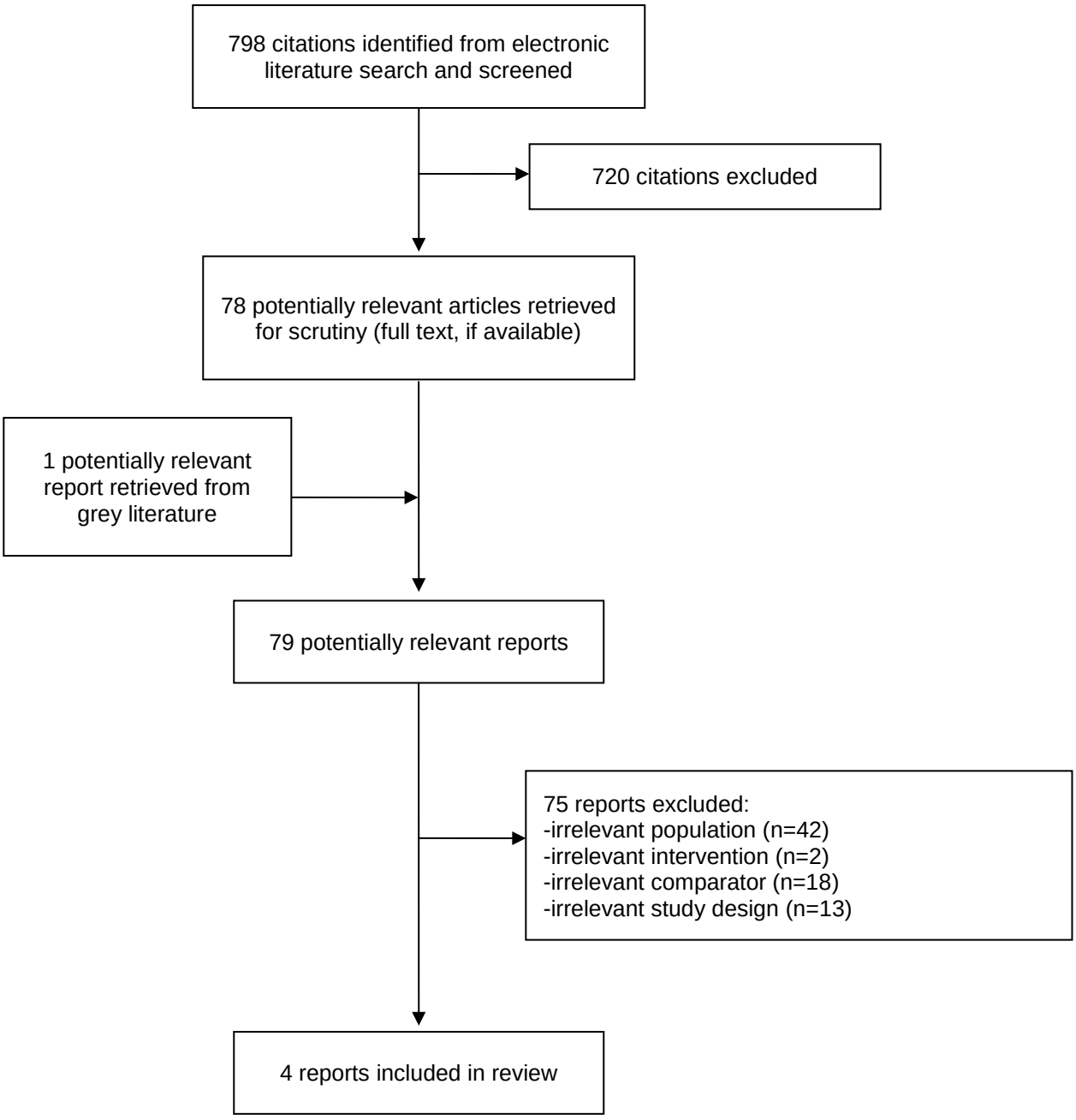
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Katoh, 2018,[15] Japan	Retrospective, two-centre comparative cohort study	Patients (n = 20) diagnosed with adrenal metastatic tumors treated without the use of concurrent chemotherapy between 2004 and 2017 (1 woman, 19 men). Median age for intervention group: 65 (range: 48 to 86) years Median age for control group: 66 (55 to 80) years	Intervention: general-SBRT Comparator: RTRT	Overall survival rates, local control rates, adverse events Median follow-up: 17.5 months
Lodeweges, 2017,[16] The Netherlands	Retrospective, one-centre comparative cohort study	Patients (n = 110) who received a recommendation at the centre's multidisciplinary thoracic tumor board for a local metastasis-directed treatment with curative intent for pulmonary metastases between 2007 and 2010 (46 women, 64 men) Median age for intervention group: 70 (range: 49 to 89) years Median age for control group: 61 (range: 18 to 80) years	Interventions: SABR Comparator: pulmonary metastasectomy	Overall survival, freedom from failure of local strategy, progression-free survival, freedom from local progression Median follow-up: 7.6 (5.8 to 9.8) years
Filippi, 2016,[17] Italy	Retrospective, one-centre, comparative cohort study	Patients (n = 170) with stage IV oligometastatic colorectal cancer treated at the time of their first diagnosis of lung oligometastases with either surgery or SBRT in the time interval 2005 and 2012 (69 women, 101 men) Median age for intervention group: 72.07 (IQR: 66.06 to 77.03) years Median age for control group: 66.37 (IQR: 59.29 to 72.38) years	Interventions: SBRT Comparator: lung metastasectomy	overall survival, progression-free survival Median follow-up: 27 (16.1 to 71.7) months for SBRT; 45.8 (13.6 to 107.1) months for lung metastasectomy

IQR = interquartile range; RTRT = real-time tumor-tracking radiotherapy; SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiotherapy

Table 2: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparators	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Lester-Coll, 2016,[18] USA	Cost-effectiveness, 1-month cycle length, 5-year time horizon; USA societal perspective	To evaluate this potential transition in the treatment of oligometastatic disease from systemic therapy to technologically advanced local therapy; a cost-effectiveness analysis of VATS wedge resection, SBRT, and systemic therapy for pulmonary oligometastases in patients with melanoma, NSCLC, and colon cancer	5 different cohorts of patient disease: 1. melanoma 2. NSCLC AC 3. NSCLC EGFRm AC 4. NSCLC SCC 5. colon cancer	Intervention: SBRT Comparators: VATS wedge resection Systemic therapy	Markov model	Model parameters and cost derived from several records (>30 referenced sources)	Societal WTP was defined at $100,000 per QALY gained

AC = adenocarcinoma; EGFRm = epidermal growth factor receptor mutated; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life years; SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma; USA = United States of America; VATS = video assisted thoracic surgery; WTP = willingness-to-pay

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
Katoh, 2018[15]	
• Objectives, intervention, comparator, and main outcomes of the study clearly described • Outcomes of interest graded using a recognized scale (i.e., Revised Response Evaluation Criteria in Solid Tumors Guideline, version 1.1; Common Terminology Criteria for Adverse Events, version 4.0) • Appropriate statistical tests used to assess outcomes • Characteristics of the study population clearly described • Main findings of the study adequately described • Actual probability values (*P* values) reported for main outcomes that are larger than $P < 0.001$ • Due to the type of outcome being assessed (i.e., acute and late adverse effects), adverse events reported • Funding for the study clearly stated and authors declared potential conflicts of interest	• No mention of blinding evaluators who ascertained outcome data • Due to the type of study design, randomization and blinding of participants not possible • Sample size for statistical power not calculated • Patients in the RTRT group came from Hokkaido University only (n = 12) whereas the general-SBRT group came from both Hokkaido University (n = 3) and the University of Yamanashi Hospital (n = 5) • It is unclear whether the participants were representative of the source population • It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive • Median length of follow-up reported for all patients but not explicitly reported by group • Distributions of potential confounders not described; therefore, no analysis performed to adjust for potential confounders • Estimates of the random variability not provided (e.g., 95% confidence intervals)
Lodeweges, 2017[16]	
• Objectives, intervention, comparator, and main outcomes of the study described • Patients in both groups from the same centre • Appropriate statistical tests used to assess outcomes • Characteristics of the study population clearly described • Main findings of the study described • Actual probability values (*P* values) reported for main outcomes that are larger than $P < 0.001$ • Estimates of the random variability provided as 95% confidence intervals	• No mention of blinding evaluators who ascertained outcome data • Due to the type of study design, randomization and blinding of participants not possible • Sample size for statistical power not calculated • It is not clear if the outcomes of interest were graded using recognized scale(s) • It is unclear whether the participants were representative of the source population • It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive • Median length of follow-up reported for all patients but not explicitly reported by group • Funding for the study no reported; no conflicts of interest statement included in publication
Filippi, 2016[17]	
• Objectives, intervention, comparator, and main outcomes of the study clearly described • Outcomes of interest graded using a recognized scale (e.g., Common Terminology Criteria for Adverse Events version 3.0)	• No mention of blinding evaluators who ascertained outcome data • Due to the type of study design, randomization and blinding of participants not possible • Sample size for statistical power not calculated

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
• Patients in both groups from the same centre • Characteristics of the study population clearly described • Main findings of the study adequately described • Appropriate statistical tests used to assess outcomes • Actual probability values (*P* values) reported for main outcomes that are larger than $P < 0.001$ • Estimates of the random variability provided as 95% confidence intervals	• Length of follow-up different between groups • It is unclear whether the participants were representative of the source population • It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive • Authors state there is a risk of incomplete control of confounding factors because of the retrospective and observational nature of the study • Funding for the study no reported; no conflicts of interest statement included in publication

RTRT = real-time tumor-tracking radiotherapy; SBRT = stereotactic body radiotherapy

Table 4: Strengths and Limitations of Economic Study using the Drummond Checklist[13]

Strengths	Limitations
Lester-Coll, 2016[18]	
• The research question, its economic importance, the viewpoint of the analysis, and the rationale for choosing the interventions stated • The form of economic evaluation is stated and justified in relation to the question addressed • The sources of effectiveness estimated are explicitly stated • The primary outcome measure for the economic evaluation is stated • Sources and methods used for estimating costs are stated • The currency used for all costs (i.e., United States Dollar) was stated • The alternatives being compared were described in appendix • Details of the models are given and the key parameters are justified • The time horizon is stated • Details of statistical methods and approaches to sensitivity analyses are provided • Quality-adjusted life years were calculated and incremental cost-effectiveness ratios were calculated in scenarios where there was no dominant strategy • Costs were discounted with 3% per annum (described in appendix) • The choice of variables for sensitivity analysis is justified; ranges for sensitivity analysis are provided • The conclusions follow from the data reported and are clearly stated with appropriate limitations identified	• It is uncertain if these findings can be applied to the local population (i.e., Canada)

Appendix 4: Main Study Findings and Authors' Conclusions

Table 5: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Katoh, 2018[15]	
Overall survival No significant difference between RTRT and general-SBRT groups (P = 0.60) Local control Significant difference between RTRT (100% at 1 year) and general-SBRT groups (50% at 1 year; P < 0.001) Adverse effects Acute adverse effects: • Grade 2: 4 patients in RTRT group, 0 patients for general-SBRT group • Grade 3-5 : 0 patients for either group Late adverse effects: • Grade 2-5 : 0 patients for either group	"*This study showed that although both treatments are safe and effective, the real-time tumor-tracking radiotherapy is more effective than general stereotactic body radiotherapy in local control for adrenal metastasis*."(p.1)[15] "*In conclusion, this study further strengthened our previous observation that precise radiotherapy methods, such as RTRT and general SBRT, can provide safe and effective treatment for selected patients with adrenal metastasis while meeting the dose constraints for critical organs around the adrenal glands. For most oligometastatic patients with adrenal metastatic tumors, these treatments should be regarded as an alternative to surgical resection. It should be noted that RTRT showed significantly higher LC rates than general SBRT, and a few tumors demonstrated a complete response after the RTRT without serious adverse reactions."* (p.8)[15]
Lodeweges, 2017[16]	
5-year overall survival No significant differences between SABR and PME groups Freedom from failure of local strategy No significant differences between SABR and PME groups Progression-free survival No significant differences between SABR and PME groups Freedom from local progression No significant differences between SABR and PME groups	*"Despite treatment selection clearly disadvantaging SABR against surgery, even unadjusted outcome was not better when pulmonary oligometastases were surgically removed rather than irradiated."* (p. 1442)[16] "*The present analysis does not support favoring surgery over SABR; but still, it also does not provide direct evidence for using either resection or SABR for oligometastases. Rigorous research comparing a primarily local treatment strategy with nonlocal treatment strategies is urgently needed to better characterize patients who might benefit from aggressive local treatment of lung metastases with the intention of cure or, at least, postponement of systemic treatment for as long as possible. In addition and complementary to that strategy, in an era of increasing use of molecularly targeted agents and immunotherapy for metastatic disease, there is a need for characterization of situations in which local metastasis-directed treatment would supplement such systemic treatment by effectively tackling localizable treatment resistance"* (p. 1444-5)[16]
Filippi, 2016[17]	
Overall survival No significant difference between SBRT and surgery groups at 1 year and 2 years (P = 0.134) Univariate and multivariable Cox models did not discern a clear treatment effect on overall survival (adjusted $HR_{SBRT\ versus\ surgery}$ = 1.71; 95% CI, 0.82 to 3.54; P = 0.149) and smaller differences using the inverse probability treatment weighting method ($HR_{SBRT\ versus\ surgery}$ = 1.28, 95% CI, 0.58 to 2.82; P = 0.547).	*"With limitations consisting in the retrospective observational design and different sample sizes, the results of this explorative analysis indicate that overall survival probability after SBRT is similar to surgery for the first 2 years from treatment. This finding supports the need for high-quality trials comparing different treatment modalities for lung oligometastases from CRC."* (p. 505)[17] *"This retrospective study suggests that patients treated with*

Table 5: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Progression free survival Indeterminate due to different follow-up protocols applied to the two cohorts	*SBRT for CRC lung oligometastases could achieve overall survival rates at 2 years comparable with surgery. These findings are challenging, confirm previous results and support the need for high-quality trials comparing currently used treatment modalities such as SBRT, radiofrequency ablation and surgery versus systemic therapies or observation in order to inform this important treatment decision."* (p. 510)[17]

CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; LC = local control; PME = pulmonary metastasectomy; SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiotherapy; RTRT = real-time tumor-tracking radiotherapy

Table 6: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion

Lester-Coll, 2016[18]

Table 4. Base case results: expected costs, QALYs, and ICERs for non-dominant strategies*

Histology	Treatment arm	Net cost (USD$)	Net QALYs	ICER, $ value, per 1 QALY
Melanoma	SBRT	467,787	0.85	
	Wedge resection	491,359	0.83	3,494,568 (ref: SBRT)
	Systemic	619,493	0.87	7,585,316 (ref: SBRT)
NSCLC AC	SBRT	156,725	0.80	Dominant
	Wedge resection	164,431	0.78	
	PacCB	185,419	0.68	
NSCLC SCC	PacC	123,799	0.48	
	SBRT	136,590	0.49	902,849 (ref: PaaC)
	Wedge resection	144,113	0.48	
NSCLC EGFRm AC	Erlotinib	147,091	1.90	
	SBRT	152,459	1.94	126,303 (ref: erlotinib)
	Surgery	162,445	1.92	801,097 (ref: erlotinib)
Colon	Wedge resection	147,723	2.14	Dominant
	SBRT	162,753	2.12	
	FOLFOX	168,864	1.60	

Abbreviations: AC = adenocarcinoma; EGFRm = epidermal growth factor receptor mutated; FOLFOX = fluorouracil plus oxaliplatin; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; PacC = paclitaxel/ carboplatin; QALY = quality-adjusted life year; SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma.

Table 5. Significant sensitivity analyses (WTP = $100,000/QALY)*

				ICER	
Histology	Parameter	Range studied	Threshold	Lower boundary	Upper boundary
Melanoma	Utility s/p SBRT	0-1	0.41	pembrolizumab	SBRT
NSCLC AC	Utility s/p SBRT	0-1	0.57	PacCB	SBRT
NSCLC SCC	Cost SBRT	5000-30,000	$9459	SBRT	PacC
	Utility chemo lung	0-1	0.59	SBRT	PacC
NSCLC EGFRm AC	P erlotinib diarrhea	0.8-3	2.5%	Erlotinib	SBRT
	HR PFS erlotinib	0.10-0.54	0.14	SBRT	Erlotinib
	Utility s/p SBRT	0-1	0.87	Erlotinib	SBRT
	Utility erlotinib	0-1	0.64	SBRT	Erlotinib
Colon	Utility s/p wedge resection	0-1	0.61	SBRT	Resection

Abbreviations: AC = adenocarcinoma; EGFRm = epidermal growth factor receptor mutated; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; P = probability of; PacC = paclitaxel/ carboplatin; PacCB = paclitaxel/ carboplatin/ bevacizumab; QALY = quality-adjusted life year; s/p = status post; SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma; WTP = societal willingness-to-pay.
* Total costs = initial therapy + second line therapy + adverse events + hospice care. QALYs are lifetime estimates.

"Our study demonstrates that SBRT or wedge resection can be a cost-effective initial management strategy in patients with pulmonary oligometastatic disease, and should be considered in favorable prognosis patients able to tolerate treatment. Despite potential increases in survival associated with systemic therapy (e.g., pembrolizumab), such therapies were not cost effective in this model when local treatment options were available, due the high cost of systemic therapy. Systemic therapy was only cost effective when costs were comparatively low, as in the case of SCC. Prospective trials will be needed to validate these findings and assess the impact of how improved local control with SBRT or surgery can improve outcomes in oligometastatic cancer. Nonetheless, the consideration of local therapy as a cost-effective option represents a sea change in the treatment of oligometastatic disease." (p. 669-70)[18]

* Reprinted from Int J Radiation Oncol Biol Phys, Vol 95, Lester-Coll et al., Cost-Effectiveness of Surgery, Stereotactic Body Radiation Therapy, and Systemic Therapy for Pulmonary Oligometastases, pp. 663-672, Copyright (2016) with permission from Elsevier."

SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma

Appendix 5: Additional References of Potential Interest

Population may include patients with oligometastatic cancer, but definition unclear or not explicitly stated

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