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Is SABR cost-effective in oligometastatic cancer? An economic analysis of SABR-COMET randomized trial

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Abstract

The phase II randomized study SABR-COMET demonstrated that in cancer patients with 1-5 oligometastatic lesions, stereotactic ablative radiotherapy (SABR) was associated with an improvement in both progression-free survival and overall survival compared to standard of care (SoC). SABR, however, is associated with higher costs and treatment-related toxicity. The objective of this study was to assess the cost-effectiveness of SABR versus SoC in patients with oligometastatic disease.

A time-dependent Markov model with five health states was constructed from the Canadian health care system perspective. Utility values and transition probabilities were derived from the SABR-COMET trial. Costs were obtained from the published literature. A willingness-to-pay threshold of $100,000/quality adjusted life year (QALY) was used.

SABR was cost-effective in the base case, at an incremental cost-effectiveness ratio of $37,157/ QALY gained over a lifetime horizon, as compared to the SoC. Therefore, administering SABR is cost-effective for patients with 1-5 oligometastatic lesions compared to SoC.

Keywords

cost-effectiveness, stereotactic ablative radiotherapy (SABR), oligometastases

Summary for lay audience

Historically, cancer that has spread beyond its origin, a state known as metastatic disease, is treated with medications such as chemotherapy that go throughout the body. Radiotherapy, as a form of local treatment, has been traditionally used to palliative symptoms. Two major developments have resulted in a paradigm change. First, there is an increasing appreciation of the concept of oligometastatic cancer, whereby, patients with a limited number of metastases have been observed to have an improved prognosis. Secondly, the recent phase II SABR-COMET trial demonstrated that stereotactic ablative radiotherapy (SABR) delivering a high dose of radiation precisely, can improve cancer control and potential survival for patients with oligometastatic cancers.

SABR is associated with more treatment-related side effects and requires more health resources. It is unknown whether the additional cost is justified by the potential health benefit gained from SABR. Therefore, this study aims to assess the cost-effectiveness of adding SABR to the standard of care (SoC) in these patients, from the perspective of the Canadian health care system.

We developed a Markov model simulating a cohort of hypothetical patients based on the SABR-COMET trial. The model took considerations of survival, cancer progression, treatment-related side effects, utilities (indicators of quality of life), and medical care costs. The model reported the incremental cost-effectiveness ratio (ICER) of SABR, which is defined by the difference in cost divided by the difference in quality-adjusted life years (QALYs) comparing the two treatment approaches.
Our model predicted that SABR+SoC was cost-effective compared to SoC, with an ICER of $37,157/QALY. This is below the commonly accepted willingness-to-pay threshold of $100,000/QALY, which represents an estimate of what a consumer of health care might be willing to pay for the health benefit given other competing demands on that consumer's resources. The robustness of our findings was assessed via sensitivity analysis (SA) by varying parameters over plausible ranges individually (deterministic one-way SA) and simultaneously (probabilistic SA). Based on extensive testing, we conclude that the findings of this model are robust.

In conclusion, SABR+SoC is cost-effective compared to SoC for patients with oligometastatic cancer from the Canadian health care perspective.

Co-Authorship Statement

This thesis contains materials from unpublished manuscript.

Alexander V. Louie, Gregory S. Zaric, David A. Palma, X. Melody Qu, and Yujie Chen contributed to the study design.

X. Melody Qu and Yujie Chen contributed to data collection, analysis and model construction.

X. Melody Qu contributed to the initial draft of the manuscript.

All authors (X. Melody Qu, Yujie Chen, Gregory S. Zaric, Suresh Senan, Robert A. Olson, Stephen Harrow, Ava John-Baptiste, Stewart Gaede, Liam A. Mulroy, Devin Schellenberg, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Andrew Warner, George B. Rodrigues, David A. Palma, Alexander V. Louie) contributed to interpretation, and editing of the manuscript.

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1.1.1 Oligometastasis

The oligometastatic state was first proposed in 1995, and refers to an intermediate disease state, between localized primary tumor and widespread dissemination of cancer, whereby cancer has only spread to a limited number of metastatic sites [1]. Generally speaking, oligometastases refers to 5 or fewer metastases, and can be further defined as either synchronous or metachronous. Synchronous oligometastases indicates that the spread of cancer and the primary tumor are diagnosed at the same time, while metachronous oligometastases refers to when the metastases occurs after the primary tumor has been treated [2].

The initial reports on the use of ablative local treatments for oligometastases were surgery. Early surgical experiences reported longer disease control and survival benefit for metastasectomy in liver for patients with breast cancer, pulmonary metastasectomy in patients with various of primary cancer, as well, resection of brain metastasis in patients with lung cancer and other various cancer types [3-5]. However, the local therapies such as surgery which are more aggressive may result in a higher risk of treatment-related toxicities and a decrease in quality of life. In contrast, local treatment with newer radiotherapy (RT) technology, such as stereotactic ablative radiotherapy (SABR), has been increasingly investigated, given that it is time-saving, technically feasible, potentially equally effective, as well as associated with limited adverse events and no need for post-operative recovery [6].

1.1.2 SABR

In stage IV cancers, the role of RT has historically been limited to more conservative dose fractionations, using conventional RT for the purposes of relieving symptoms and/or

preventing cancer-related complications. In contrast, SABR (also known as stereotactic body radiotherapy or SBRT), is characterized by the precise delivery of high radiation doses within a few fractions [7, 8]. Typically, SABR is delivered in 3 to 8 fractions within 1- 2.5 weeks, while conventional RT requires more than 4 to 6 weeks to deliver 20-30 fractions daily [7]. Reported 1, 2 or 3-year rates of local control with SABR are excellent, and for lung targets, are consistently around 90% [9-12]. Besides its convenience, SABR is generally well tolerated across body targets. However, given the high doses employed, caution needs to be exercised when lesions are in close proximity to organs at risk [7, 8]. Examples of serious toxicity include: major bleed, radionecrosis in the brain, permanent damage to nerves, and fistulisation along gastrointestinal tracts, major vessels, or airways etc. [6, 13].

SABR is increasingly being used as a locally curative treatment for various early stage cancers, particularly when a patient's comorbidities may increase surgical risks [9, 10, 14]. As SABR is well tolerated, convenient and potentially associated with fewer risks than surgery, its role in operable early stage cancer patients is an active area of investigation. One example of this is for early stage lung cancers [10, 15].

For oligometastases, the use of SABR is becoming increasingly popular, as patients and clinicians alike are embracing locally aggressive treatments that may incur health benefits. Reports of SABR for oligometastases have generally been limited to observational studies, which describe excellent local control rate as well as survival; however, these are highly selected patients [16-18]. Single arm prospective trials have provided a higher level of evidence, however, still need to be considered in the context of a lack of appropriate controls [19, 20]. Given the lack of randomized data in this context, a phase II, randomized controlled trial "SABR-COMET" was launched internationally, and has since completed accrual.

1.1.3 SABR plus standard of care (SoC) for oligometastatic cancer treatment

The SABR-COMET Trial (Clinicaltrials.gov identifier: NCT01446744) is a phase II randomized controlled trial. The primary aim of the trial was to evaluate treatment effect

of comprehensive treatment (SABR + SoC), as compared to SoC alone in the management of oligometastases [21, 22]. SoC referred to a set of cancer interventions that were widely used for stage IV metastatic cancer, for example, palliative radiation therapy (RT) and systemic therapy, which mainly included chemotherapy according to the earlier cancer management protocols, whereby newer agents such as targeted therapy or immunotherapy were less commonly used. A total of 99 patients with previously definitively treated primary tumors and metachronous oligometastatic disease were randomly assigned in a 2:1 ratio to the comprehensive treatment group and standard of care group, respectively. Patients were recruited from ten centers across Canada, the Netherlands, the United Kingdom, and Australia. The trial cohort consisted various cancer types, most commonly, lung, prostate, colorectal, breast cancers, among others. The number of metastases were no more than 5 per patient and up to 3 metastases within any organ system [21, 22]. Summary of patients' baseline characteristics are provided in Table 1.

In the 5-year follow up, 34 out of 66 patients (52%) of the SABR group received palliative systemic therapy, compared to 19 out of 33 patients (58%) in the SoC group. Comprehensive SABR was associated with less further palliative RT use than the SoC arm, 13 patients (20%) vs 21 patients, (64%). SABR was associated with an absolute increase of 26% (95% CI 10–41) in lesional control, defined as the proportion of metastatic lesions that are progression-free as compared to the baseline. The proportion of lesional control was 75% (75 of 100 assessable lesions) versus 49% (28 of 57 assessable lesions) in the SABR versus control group (p=0·0010). The long-term survival, quality of life (QoL) based on Functional Assessment of Cancer Therapy: General, Version 4 (FACT-G v. 4) scales [23], and adverse effects were measured every 3 or 6 months for up to 5 years. The major findings of the trial are summarized in Table 2. The Kaplan-Meier curves summarizing overall survival and progression-free survival are shown in Figure 1.

Table 1: Patients' baseline characteristics of SABR-COMET trial

Characteristic	SABR Arm (n=66)	Control Arm (n=33)
Gender, n (%)		
Male	40 (61)	19 (58)
Female	26 (39)	14 (42)
Age, mean ± SD, years	66.3 ± 11.2	68.0 ± 10.9
Average number of Metastases, mean ± SD	1.9 ± 1.1	1.9 ± 0.9
Primary Site, n (%)		
Breast	13 (20)	5 (15)
Colorectal	9 (14)	9 (27)
Lung	12 (18)	6 (18)
Prostate	14 (21)	2 (6)
Other	18 (27)	11 (33)

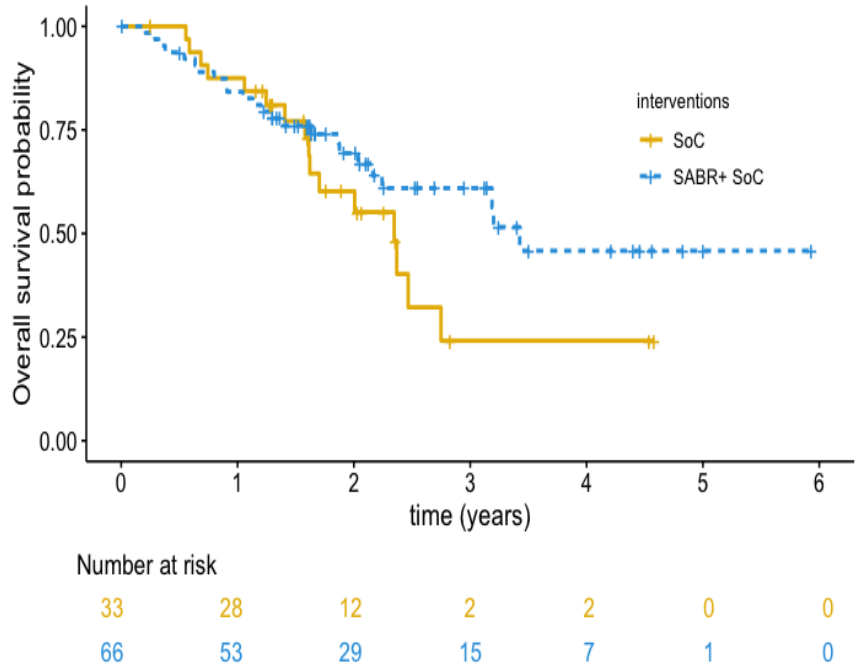
Abbreviations: SoC, standard of care; SABR, stereotactic ablative radiotherapy; SD, standard deviation

Table 2: Summary of effectiveness and safety outcomes from the SABR-COMET trial

	SABR+SoC (n=66)	SoC (N=33)	P value
Effectiveness			
All-cause mortality n, (%)	24 (36%)	16 (48%)	
mOS, (95%CI), months †	41 (26.0, not reached)	28 (19, 33)	0.09
mPFS (95%CI), months ‡	12 (6.9-30.4)	6.0 (3.4-7.1)	0.0012
HRQoL, mean (SD) ¶	82.6 (16.6)	82.5 (16.4)	0.99
Safety			
AE (Grade=5), n (%) €	3 (4.5%)	0 (0%)	
AE (Grade≥2), n (%) €	19 (29%)	3 (9%)	0.026

Abbreviations: SoC, standard of care; SABR, stereotactic ablative radiotherapy; SD, standard deviation
† mOS: median overall survival. HR (SABR+SoC vs SoC): 0.57, 95% CI (0.30–1.10); stratified log-rank p=0·090.
‡ mPFS: median progression-free survival. HR (SABR+SoC vs SoC): 0.47, 95% CI (0.30–0.76); stratified log-rank p=0·0012.
¶ HRQoL: health-related quality of life, defined as the overall mean score of Functional Assessment of Cancer Therapy: General (FACT-G) at 6th month.
€ AE: treatment-related adverse events, from grade 1 to 5, are ordered as mild, moderate, severe, life threatening or disabling, death-related, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC-AE) version 4.

a)



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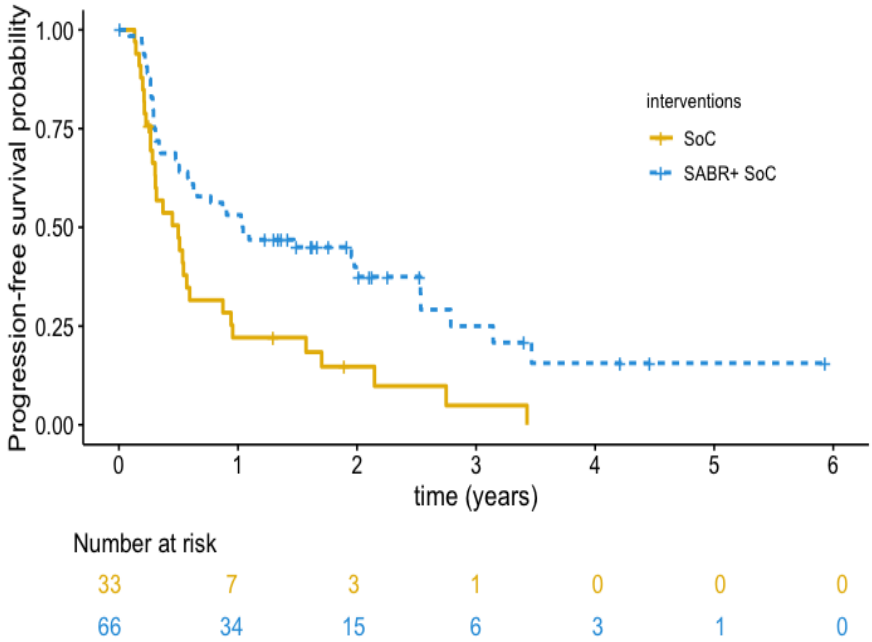


Figure 1. a) Kaplan-Meier Curve for overall survival (OS) and b) progression-free survival PFS from the SABR-COMET trial

PFS: HR (SABR+SoC vs SoC): 0.47, 95% CI (0.30–0.76); stratified log-rank p=0·0012. OS: HR (SABR+SoC vs SoC): 0.57, 95% CI (0.30–1.10); stratified log-rank p=0·090. The risk of progression or death in the SABR+SoC arm is 53% lower than the risk in the SoC arm at any time points during the follow-up. The immediate risk of death in the SABR+SoC arm decreased by 43% compared to the SoC arm.

The SABR-COMET trial has demonstrated that adding SABR to the standard of care improved median progression-free survival from 6 to 12 months (p=0.0012) and median overall survival from 28 to 41months (p =0.090). Since SABR-COMET trial pre-specified a two-sided level of significance at 0.2 using a randomized phase II screening design [22], the change in the median progression-free survival as well as the median overall survival are statistically significant ($p < 0.2$). The early censoring was most likely caused by patients' dropouts as well as more limited follow-up for patients who enrolled towards the end of the trial accrual (i.e. some patients may have had only one- or two-year follow-up at the time of data analysis). SABR was associated with an absolute increase of 26% (95% CI 10 to 41) in lesional control (the absence of progression in the assessable lesions that presented initially at randomization), without compromising quality of life (overall mean FACT-G scores at 6 months were 82.6 versus 82.5 in the SABR versus control group, p=0.99). However, there were more grade 2 or higher treatment related adverse events in SABR+SoC arm compared to the SoC arm. Despite treatment-related death (grade 5 toxicity) occurring in three out of 66 patients (4.5%) after SABR versus none in the control group, there was still a survival benefit observed in the SABR arm.

While the SABR-COMET trial suggests that comprehensive SABR is associated with increased health benefits, SABR is resource-intensive and associated with increased costs due to the complexity of the treatment. Performing SABR is more resource intensive, due to additional steps in dosimetry, quality assurance, and pre-treatment preparation. This requires additional time from personnel including radiation therapists, physicists, as well as resources such as the treatment planning system and the linear accelerator as compared to palliative RT. Therefore, in order to determine the optimal intervention from a health economic and societal point of view, the costs, patients' values, adverse effects as well as the health benefits all need to be considered in order to determine the value of this strategy. Thus, the objective of this thesis is to perform a cost-effectiveness analysis to address whether the increased costs associated with SABR are justified by the potential effectiveness gained, in the context of the Canadian health care system.

1.2 Cost Effectiveness Analysis

The purpose of a cost-effectiveness analysis (CEA) is to help prioritize different healthcare strategies to maximize the health benefits based on limited financial budgets and societal resources. This type of analysis promote the value of medical decisions and healthcare strategies by informing rational investment on interventions that generate the highest health values compared to a set of alternatives [24, 25].

Trial-based and model-based methods are the two most common methods for cost-effectiveness analyses [26]. Both methods can be applied to estimate the incremental cost effectiveness ratio (ICER) and uncertainties. While a trial-based method typically utilizes individual, patient-level costs and health outcomes prospectively collected directly from the clinical trial, model based-methods estimate these from existing data from various sources. In this context, the uncertainty is measured according to different assumptions, and is subject to increased flexibility [27]. In the SABR-COMET clinical trial, costs and utility data were not directly collected. Therefore, while a model-based method was utilized in this CEA, individual patient data from the SABR-COMET trial, along with existing data from the broader literature were utilized to inform the model. Sensitivity analyses were performed to capture the potential uncertainties and ensure internal validity.

1.2.1 Quality-adjusted life year and utility

The quality-adjusted life year (QALY) is a measure of outcome that weighs survival according to the health-related quality of life within that time period. The weight, also known as value index, ranges from 0 (death) to 1 (perfect health), and is elicited from the general population to represent public preference. This is reflected in a term known as a utility, which is a preference-based interpretation of quality of life related to a health state. [28, 29]. It incorporates not only the length of life, but also the extent to which people value their quality of life. Multiplying the utility by length of life, the health consequence associated with the intervention can be measured quantitatively and qualitatively through QALYs, given by

$$\text{Total QALY} = \sum_{t=1}^{T} q_t,$$

q_t: QALY gain in year t, $0 \leq q_t \leq 1$; T: length of time horizon.

In a CEA, the quantity of life as a clinical outcome is not sufficient to characterize the complex health consequences. Trade-offs are made simultaneously between quality and quantity of life, health benefits and adverse effects, as well as cost and health effects to determine the optimal intervention. For cancer treatment specifically, extending life expectancy as well as improving quality of life are both important. In addition, the patients' values and public values, such as taxpayers and other healthcare recipients, should be involved in determining the utility of an intervention. In other words, an intervention may benefit a proportion of individuals, but at the cost of the others [30]. Therefore, the utility, public preference is generally recommended to inform the optimal treatment [30]. QALYs facilitate comparison between an intervention and its alternatives by integrating benefits, harms and societal preference into a single scale.

There are generally three ways to directly measure the utility of an intervention: Time Trade-off (TTO), Standard Gamble (SG), and Visual Analog Scale (VAS) [30]. The TTO method asks individuals how many years in their currently impaired health state they would be willing to "trade off" in order to regain a full health. The more time a participant is willing to sacrifice to exchange for full health, the less an impaired health states would be valued, and therefore the current health state is associated with a lower utility. The SG method asks individuals to choose between the result of remaining impaired health state without receiving an intervention and the consequence of taking an intervention whereby full health gained at a risk of death. The utility would be determined by the maximal risk of death they would accept given their current impaired health state, in order to gain a full health. The more severe the impaired health condition is, the higher risk participants would be willing to take to avert it and the utility of the health state would be lower. TTO and SG methods require special training on investigators and therefore are resource intensive.

The VAS approach asks participants to rate their health states visually on an illustrated scale ranging worst to best. A score between 0 to 100 is obtained base on direct measurement from the illustrated scale. However, the scaling bias, whereby the extremes (perfect vs. poor health) of conditions are poorly represented in general, is a limitation of the method.

Nevertheless, TTO, SG and VAS have not been commonly used in the context of clinical trials. In addition to the practical and methodological concerns raised above, the patient-based preference derived by these direct measuring methods can be inconsistent with the public preference [30]. For instance, patients with chronic illness such as cancer are likely to adapt to the impaired health states so that their self-perceived health states utilities may be overrated compared to the utility value elicited from the general population [30]. Such difference may therefore mask the utility change due to health interventions. Furthermore, the public-based preference has been recommended in health economic evaluation since it is unlikely to be biased and the investment on a new strategy can impact the general public interest [30].

Generic preference-based instruments, such as EuroQol (EQ-5D), the Short Form 6D (SF-6D), and the Health Utilities Index (HUI) have been widely used to estimate health utilities in clinical research. These instruments facilitate the measuring of utilities by linking different questionnaires with the generic preference-based score to form a standardized scale, and thus are applicable to cancer clinical trials to estimate health utilities. Among them, the EQ-5D is the most widely used in cost-effectiveness analysis and has been recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK). The EQ-5D consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The scores of the five dimensions can either be used as a measure for HRQoL or be converted into a utility value based on the country-specific value sets. The value sets are generated via TTO or VAS approach within valuation studies in different countries. The EQ-5D-3L includes 3 levels in each dimension: no problems, some problems, and extreme problems. A newer version of the instrument, the EQ-5D-5L, consists of 5 levels of perceived problems per dimension and therefore the latter improves the sensitivity and reduces the celling effect

[31]. The EQ-5D can identify a total of 245 health states and previous work by Dolan et al. have estimated the utility score for each health state via TTO methods among UK adults [32]. Similarly, HUI and SF-6D assess different dimensions from EQ-5D, for which previous work have also elicited the utilities via SG accordingly among adults from Canada and the UK, respectively [30].

Although the generic preference-based instruments can be easily applied in clinical trials, they may not be sensitive enough to capture small but meaningful disease-specific changes. Therefore, the condition-specific measures are routinely incorporated in measuring the health-related quality of life (HRQoL) associated with a specific condition or disease [30]. These commonly used HRQoL instruments have been extensively studied and validated in various patients' population [23]. For instance, the HRQoL of patients with oligometastatic cancer in the phase II SABR-COMET trial were measured via the Functional Assessment of Cancer Therapy-General (FACT-G) scale, and these can then be used to generate health states utilities via mapping/cross-walking as described in the next section.

1.2.2 Mapping algorithms to estimate utilities

"Mapping", also called "cross-walking", refers to a modeling technique whereby scores from disease-specific HRQoL instruments are transformed into generic preference-based utility values [33]. HRQoL was routinely collected in SABR-COMET trial using the functional assessment of cancer therapy-general (FACT-G) scale. FACT-G is a cancer-specific instrument that consists of 4 domains that assess physical well-being, social/family well-being, emotional well-being and functional well-being of patients. Each domain includes six or seven statements. Participants are asked to score each item with an integer range from 0 (not at all) to 4 (very much), indicating the level of fitness between the statement and their conditions [23]. The HRQoL domain scores can therefore be obtained by summing up the item scores of each domain. The total score is calculated as the sum of domain scores.

There are several published mapping algorithms that have modeled conversion of FACT-G scores to EQ-5D values [34-38]. Some methods are based on the total score of the

FACT-G, while the others required to incorporate the scores of each domain, with or without adjusting for specific cancer type.

Although mapping algorithms can estimate health states utilities, these are still not truly preference-based measures as uncertainties and bias are likely to be introduced. Nonetheless, they serve as an estimate, and any parameter uncertainty can be characterised via sensitivity analysis within the CEA [39].

1.2.3 Disutilities

In addition to health states utilities, it is important to account for potential adverse events that are related to an intervention, as they may lower the health states utilities. The decrease in utilities can be accounted for via disutilities.

1.2.4 Cost of cancer care related to SABR-COMET trial

The cost of cancer management is rapidly increasing, in part due to rising medication prices, the higher incidence and prevalence of cancer and the increasing treatments prescribed. These and other factors all contribute to the cancer financial burden in Canada [40, 41]. The total direct cancer cost of Ontario in 2012 was about 5.4 billion in 2015 Canadian dollars (CAD), which is 1.8 times higher compared to the total cost of 3.0 billion (2015 CAD) in 2005. This corresponds to an annual percentage increase of approximately 8.6%. Among these cancer related health service costs, the largest expenditure increase was due to chemotherapy and RT, with an estimated annual percentage increase of 12.7% and 16.6%, respectively [41].

The total health care costs generally consist of direct costs and indirect costs. Direct costs refer to the resources needed for health care service, while indirect costs represent the losses in productivity due to illness or death. Direct costs can be further categorized as direct medical costs such as hospital care, drug, physician care etc. and direct non-medical costs which mainly include the out-of-pocket expenses such as transportation, social services, housekeeping etc.

The direct costs of cancer vary across different phases of the disease. The highest costs are incurred during the terminal phase, defined by one group as the last 12 months before

death [42]. The other 2 phases include, the initial phase, which corresponds to costs within the first 6 months of diagnosis, and the continuing care phase, which accounts for costs between the initial and terminal phases. Costs during the continuing phase are the lowest among the three phases, and this phase mainly consists of cancer surveillance as well as the managements for cancer progression or recurrence [43].

The costs of RT and chemotherapy account for about 7% and 9 % of the total continuing care costs, respectively. In contrast, during the terminal phase, RT and chemotherapy accounted for around 4% and 2% of the costs, which reflects the increased use of other supportive measures [44].

SABR delivers higher doses in fewer fractions compared to the palliative RT. Thus, it may save on direct non-medical costs related to transportation and decrease the indirect costs due to time off from work and sick leave. However, SABR is more resource-intensive than palliative RT with respect to the technical planning time required for dosimetry and quality assurance. Besides, the longer treatment delivering time per lesion also results in higher cost in SABR [45]. As an example, total direct medical costs of SABR were significantly higher than conventional fractionated radiation therapy (CFRT) as in previous studies of stage I inoperable lung cancer patients [46, 47].

The direct medical cost for RT is fully funded through individual provinces in Canada. The direct medical costs of RT can be estimated by the activity-based costing method according to descriptive costing studies. This approach divides the total spending into a series of activities-related costs, and the spending on each activity can be estimated through multiplying the unit cost of resource by the utilization of resources (i.e. time and patient volume). The total course of treatment, rather than the number of fractions, is typically employed to estimate RT costs [46].

1.2.5 Incremental Cost-Effectiveness Ratio

In order to determine whether a healthcare strategy is cost-effective or not, we employ a metric know as incremental cost-effectiveness ratio (ICER), defined as the cost difference divided by the effectiveness difference between the two compared strategies.

$$ICER = \frac{\Delta\, cost}{\Delta\, effectiveness} = \frac{cost_{(\text{SABR+SoC})} - cost_{(\text{SoC})}}{effectiveness_{(\text{SABR+SoC})} - effectiveness_{(SoC)}}$$

In a cost-utility analysis, the effectiveness is commonly measured in QALYs, and therefore ICER is the cost per QALY gain. ICER indicates the average incremental cost related to one additional unit of health benefit in health care system by shifting from one option to its alternatives. In our case, the two options are SoC alone versus SABR+ SoC strategy.

Previous studies have evaluated the cost-effectiveness of SABR versus other standard treatments in different clinical settings, such as non-small cell lung cancer (NSCLC), melanoma, colon cancer, via model-based methods [48, 49]. For example, one study compared SABR to video-assisted thoracic surgery (VATS) wedge resection and systemic therapy, as initial treatment for pulmonary oligometastases with mixed types of primary tumors, including melanoma, non-small cell lung cancer and colon cancer [48]. In this study, SABR resulted in a 0.85 QALY gain at a cost of $467,787 (2015 USD) for melanoma, as compare to the VATS wedge resection ($491,359/0.83 QALY) and immunotherapy ($ 619,493/0.87 QALY). Therefore, compared with SABR, surgery and systemic therapy were not cost-effective with an ICER value of $7,585,316/QALY and $3,494,568/QALY, respectively, given a willingness-to-pay threshold of $100,000/QALY. However, the cost-effectiveness of SABR relative to the two other strategies were inconsistent across different types of cancer. Local treatments, including SABR and surgery, were more likely to be cost-effective in cancer, whereas systemic therapies required relatively higher costs.

1.2.6 The willingness-to-pay threshold

Whether a health strategy is cost-effective or not depends on the maximum amount of money that the policy makers are willing to pay to exchange for one additional unit of QALY, given the limited financial budget and health care resources, known as the willingness-to-pay (WTP) threshold. It serves as a benchmark for the value of healthcare interventions and indicates the highest price the society would pay to exchange for one more unit of QALY [50]. The widely used WTP thresholds are based on World Health Organization (WHO) criteria, which have been inferred from the gross domestic product

(GDP) per capita and varies among different countries [51]. The NICE in the UK recommended an explicit threshold of £20,000/QALY to £30,000/QALY for examining the efficient interventions [52]. In US, there is no explicit threshold, and implicit thresholds range from 100,000–150,000 USD/QALY to help guide reasonable decisions [50]. Although the value of the threshold is not clearly stated in the Canadian Agency for Drugs and Technologies (CADTH) guidelines, currently, a threshold of either $50,000 or $100,000 per QALY have been applied, although inconsistently [53].

The ICER calculated from the CEA is compared with the WTP threshold to determine a rank of set of cost-effective interventions that help health care policy-makers to invest properly to maximize the health benefit with limit budget or minimize cost for specific health-effect [51].

In this study, a $100,000 CAD/QALY threshold for cost-effectiveness was employed. If the new strategy of interest is associated with a smaller ICER value than the threshold, it can be interpreted as the new strategy requires a below-average cost to exchange for one additional unit of QALY in the health care system, and therefore it will be considered as cost-effective.

1.3 Decision analytical modelling in the economic evaluation of health technologies

Decision analysis is a mathematical framework that serves to evaluate and determine the optimal outcome among a group of available options, with the purpose of informing decision-making according to various scenarios [24]. In health technology assessment, decision analytical models aim at helping decision-makers to understand the association between the evaluated health effectiveness and their incremental costs [54]. These models consist of variables and structures components that can simulate patterns of disease and prognosis based on evidences demonstrated by cohort studies or trials, which make it able to answer study questions where no direct evidence is currently available, and therefore, inform decisions in various uncertain situations [24].

For chronic disease and cancer with recurrent events and time dependent risks, state transition models can simplify the model structure by using health states to define the clinical process and the subsequent prognosis, rather than exhausting all the treatment options and their consequences. State transition models are recommended to solve decision problems that can be structured with discrete health states among a closed cohort, without need to account for the interactions between individuals. It may either simulate the expectancy value of an entire cohort (Markov cohort simulation) or track individual patient one at a time (Monte Carlo microsimulation) [55].

Markov model, also known as cohort state-transition model, relies on a framework of discrete, exhaustive and mutually exclusive health states representing the course of disease over time. The time horizon is divided into equally fixed intervals, known as Markov cycles. Transition probabilities indicate the risk of inter-states transition among the cohort within each Markov cycle and, as per Markovian property, are independent of the history of previous transitions (including both the transition of previous health states and the time spent in the current health state) [55, 56].

In contrast, Monte Carlo microsimulation (individual-level state transition model) is not limited by the Markovian property, as it relies on individual simulation and incorporates “tracker variables” to capture individual-level events. Whether or not an individual experience a transition is determined by a random number. However, the model is computationally intensive.

Chapter 2

2 Objective and research framework

The aim of this research was to perform a cost-effectiveness analysis to compare SABR treatment (SABR+ SoC) versus standard of care (SoC) alone in the treatment of oligometastatic cancer. Based on the SABR-COMET trial, this study investigated whether adding SABR to the current standard of care provides value from the Canadian healthcare system perspective. The main steps of this project are summarized as follow:

1) Develop a Markov model with several health states and time dependent transition probabilities to simulate the disease process of oligometastatic cancer treated by each strategy;
2) Validate the Markov model internally and externally;
3) Use quality of life data from SABR-COMET trial patients to obtain health state utilities through mapping algorithms from the published literature;
4) Estimate the cost of comprehensive treatment (SABR+ SoC) and SoC alone from the payer's perspective from previous costing studies;
5) Perform a cost-effectiveness analysis of the base case for a lifetime horizon, to inform whether the SABR-associated cost and toxicities are justified by the potential health benefit and quality-adjusted life year gained;
6) Conduct deterministic sensitivity analyses to evaluate the impact of parameter uncertainty and its effect on ICER;
7) Conduct probabilistic sensitivity analyses to evaluate the robustness of the model across multiple parameter and distribution uncertainties.

This study was reported following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline [57].

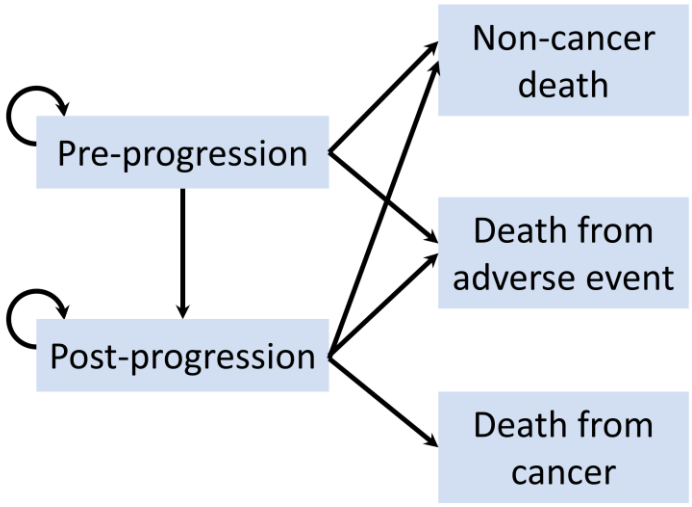
Chapter 3

3 Methods

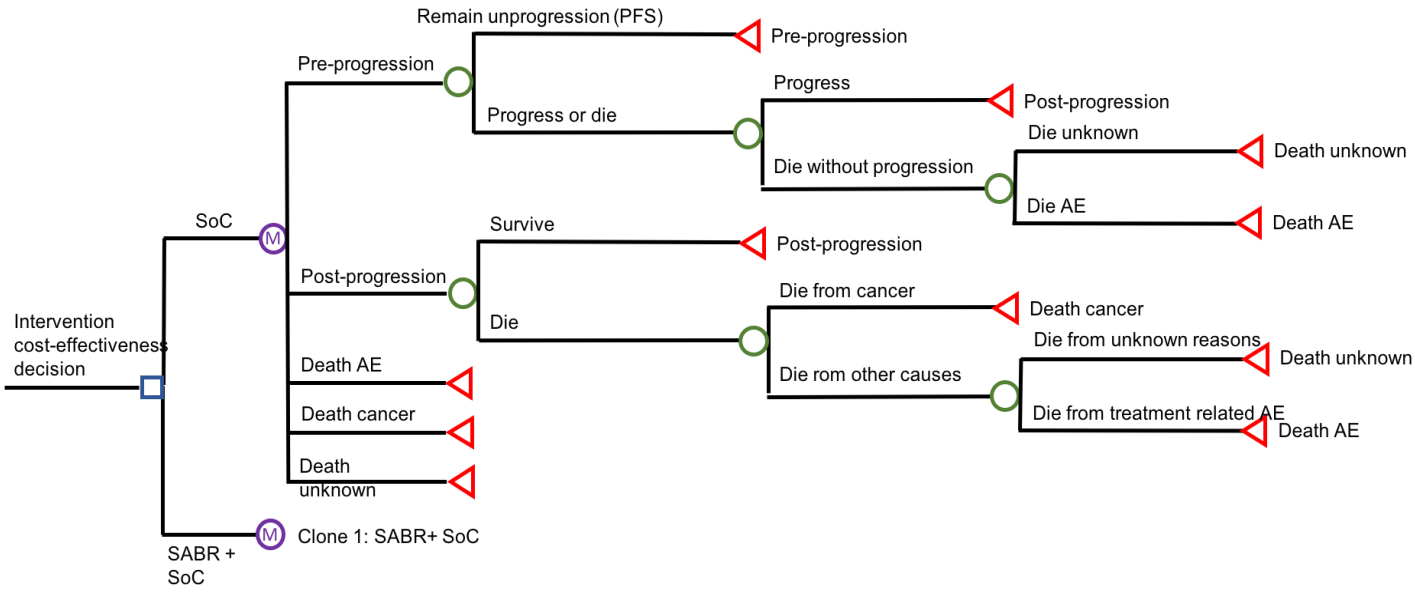
3.1 Markov model and cost-effective analysis

We constructed a Markov model using TreeAge Pro 2018 to evaluate the cost-effectiveness of SABR+ SoC vs SoC for oligometastatic cancer patients from the Canadian healthcare system perspective. This was defined as up to 5 metastatic lesions and a controlled primary tumor, which were modeled as breast, lung, colorectal, prostate, and other types of cancer. The model allowed for a hypothetical cohort of patients, whose features are similar with those in the "SABR-COMET" trial, which recruited patients from centers in Canada, the Netherlands, the UK, and Australia [22].

In the model, we defined 5 unique and discrete health states: 1) Pre-progression 2) Post-progression 3) Death from adverse event 4) Death from cancer and 5) Non-cancer death (Figure 2). All patients entered the Markov model by starting in the Pre-progression health states, representing immediately after receiving specified treatment such as SABR. As the model cycles, they either transit to another health states or remain in the same state, determined by the transition probability and the transition direction. Transition probabilities were estimated form individual-level patient data in the SABR-COMET trial for the five pre-defined health states for each cycle.



a. State transition diagram



b. Decision tree

Figure 2. Decision model for oligometastatic cancer a) State transition diagram b) Decision tree

In the model, we defined 5 unique and discrete health states: 1. Pre-progression 2. Post-progression 3. Death from adverse event 4. Death from cancer 5. Non-cancer death. All patients started beginning in the pre-progression health states. For pre-progression and post progression health states, as model cycles, a proportion of patients will remain in the same states or travel to the next potential states in each cycle based on the transition probability. Once they enter the three absorbing health states, modelled as death from cancer, death from adverse event, or non-cancer death, they cannot move anymore. The model assumed that dying before cancer progression can only be attributed to the grade 5 adverse events or other non-cancer reason. The Markov process allows health states-related rewards (costs and QALYs) to be accumulated for every circle (every 3 months). A lifetime horizon was adopted, as suggested by the Canadian Agency for Drugs and Technologies (CADTH) guidelines [58].

Both utilities and costs were discounted at an annual rate of 1.5% in base case scenario, according to the guidelines for the economic evaluation from Canadian Agency for Drugs and Technologies in Health [58]. Thus, the quarterly discount rate equals to:

$$Quarterly\ discounting\ rate = (1 + annual\ discounting\ rate)^{\frac{1}{4}} - 1.$$

Where annual discounting rate =1.5%

For each cycle, the cost and utility cycle rewards in the model were discounted as:

$$present\ value = \frac{future\ value}{(1+r)^t}$$

Where r = quarterly discounting rate,

and t= number of cycles (measured in quarters)

The willingness to pay threshold of $100,000/ QALY was applied. We used within cycle correction to avoid overcounting the cost and utility rewards (model rewards accumulated at the beginning of each cycle, while transition occurred at the end of each cycle). The cycle rewards after within cycle correction were calculated by averaging the cycle rewards (costs and utilities) calculated at the beginning and end of each cycle. The assigned rewards in the Markov model are summarized in Table 3. The definitions of the Markov rewards are listed in Appendix A.

Table 3. Summary of Markov rewards

Health states	Startup cost	Cycle cost / 3month, $	Event cost	Startup utility	Cycle utility	Event utility
SoC						
Pre-progression	palRT cost + AE cost	Continuing care cost§	0	disutility	Pre-progression utility	0
Post-progression	0	Continuing care cost§	palRT cost	0	Post-progression utility	0
Death from cancer	0	0	Δterminal care cost*	0	0	0
Death from AE	0	0	Δterminal care cost*	0	0	0
Non-cancer death	0	0	Δterminal care cost*	0	0	0
SABR + SoC						
Pre-progression	SABR cost + AE cost	Continuing care cost§	0	disutility	Pre-progression utility	0
Post-progression	0	Continuing care cost§	SABR cost + palRT cost	0	Post-progression utility	0
Death from cancer	0	0	Δterminal care cost*	0	0	0
Death from AE	0	0	Δterminal care cost*	0	0	0
Non-cancer death	0	0	Δterminal care cost*	0	0	0

All costs were adjusted to 2018 CAD. Within cycle correction were applied.
Abbreviations: SoC: standard of care; palRT: palliative RT; death cancer: death from cancer; death AE: death form adverse events; death non-cancer: death from non-cancer AE: adverse event.
§continuing care cost: health care received from diagnosis to 12 months before death. It consists of chemotherapy cost and base care cost.
*Δterminal care cost: the difference between terminal care cost (cost for the last year of life) and continuing care cost. The cost difference was added to all death-related health states as a one-time cost to account for the increased cancer care cost within the last 12 months before death as compared to the continuing care cost. The maximum value of Δterminal care cost was spent by patients survived for no less than 12 months (4 Markov cycles), according to the definition of terminal care cost [43].

Several key assumptions were made during the construction of the model, including:

1) Patients in the SABR group who developed progressive disease received additional salvage therapy with further SABR and remained in the Post-progression state;
2) The resources required for each metastatic lesion treated by SABR are considered separate and independent courses of RT;
3) Once cancer progressed, it cannot return to the pre-progression health state;
4) Dis-utilities from adverse events are assumed to be independent of the type of primary tumor.

3.2 Mapping and estimating the health states utility

Figure 3 provides an overview of the utilities and disutilities estimating methods. The detailed processes were described in the following three sections.

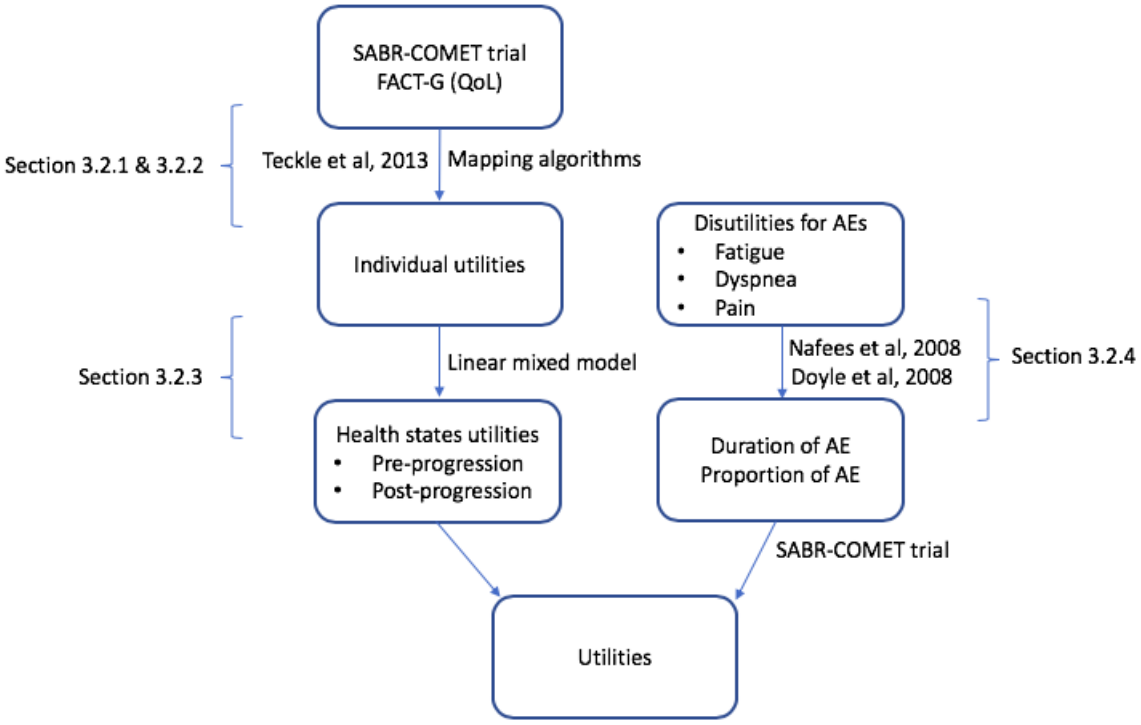


Figure 3. Overview of utilities and disutilities estimating methods

We searched Health Economics Research Centre (HERC) Database of Mapping Studies [59, 60] to identify the available mapping algorithm from studies by performing basic quality checks on the relevance of the patient population, QoL measure instruments, target utility measure instruments, and utility elicitation methods.

We selected studies whose target population shared the most similar patients' characteristics with the SABR-COMET trial. Specifically, we identified studies whereby we could convert the available QoL data from the trial, which was measured using the FACT-G scale, into health states utilities. We then performed a longitudinal analysis with the mapped individual utility data to estimate the pre-progression and post-progression utility (mean and 95% confidence interval) using linear mixed model, in which time was considered as a continuous variable.

3.2.1 Databases and literature searching

Potential available studies were included based on the two following criteria:

1. Study participants: cancer patients with mixed or single type of primary tumor.

2. Studies design: studies included the FACT-G scale as a source instrument, regardless of the type of target instrument.

The HERC Database of Mapping Studies (last accessed: 24th April 2019 [59]) was utilized, and all references within included studies were also reviewed to identify other candidate studies that may have been omitted within HERC.

3.2.2 Data collection and algorithm selection

For candidate mapping algorithms, we summarized relevant information to determine the appropriateness and relevance for our model. These factors included: the sample size of the study, demographics, model performance and FACT-G scores. The optimal study, which reported potential mapping algorithms was selected based on its relevance to the SABR-COMET patient population to minimize the difference between the mapping study and the trial regarding the study population [37].

The optimal study recommended several algorithms providing different target instrument-based utilities, such as the SF-6D based utility and the EQ-5D based utility. The algorithm that generated EQ-5D based utility was preferred because the EQ-5D is the more widely available instrument for measuring utility, and is recommended by the NICE in England for Health Technology Assessment [33].

We compared different mapping algorithms developed by the optimal study. In general, three regression model were used including the censored least absolute deviations (CLAD) approach, which is a median based model accounting for the right censoring, the generalized linear models (GLM) and ordinary least squares (OLS). All of them produced consistent utility predictions with similar accuracy according to the optimal mapping study. However, CLAD model is more complicated than GLM or OLS, and the application of median-based model for predicting utility is controversial, as it may not accurately reflect the total utility of the population at aggregate level [38]. GLM and OLS are both simple, however, GLM relaxes the assumption of OLS, and produced similar results as CLAD [37]. Since all of the three models are capable of accurately predicted utility predictions according to the mapping study. We finally chose GLM to predict health states utilities from FACT-G scores obtained from the SABR-COMET trial.

The mapping study provided a total of three GLM models. They were different in that they predicted the utilities based on various predictors, including the mean FACT-G total score alone, the mean FACT-G domain scores or combining FACT-G domain score with cancer type and stage as predictor(s). We chose the GLM model regressed utility on FACT-G domain score, cancer type and stage as predictor(s) rather than the two other GLMs regressed on FACT-G total score, or domain score only. First, the predictions using FACT-G domain scores are comparatively more accurate (a smaller RMSE) than these derived from total score as shown in the mapping study. Second, in the SABR-COMET trial, all patients are with stage IV cancer, thus including stage as a predictor may improve the accuracy of prediction. Therefore, in our study, utilities were mapped from FACT-G domain scores, stage and primary cancer type via the GLM model.

3.2.3 Estimating the pre-progression and post-progression utility

Using the published mapping algorithm, we obtained the individual level utility recorded every 3 months for first two years and every 6 months for the last three years over the trial follow-up duration. According to the methods provided by Johnson et al. [61], we performed longitudinal analyses using mixed effect model to interpret the trend of the utility change overtime, before and after progression, and compared the utility trajectory, determined by intercept and slope coefficient, between 2 intervention strategies for both pre-progression state and post-progression state. We plotted the trend of mean utilities at each visit for the 2 intervention groups, and linear relationships were observed between utility and time for both pre-progression and post-progression health states as shown in Figure 4, suggesting a linear mixed model as below,

$$Utility = \beta_0 + \beta_1 strategy + \beta_2 time + \beta_3 progression\ status + \beta_4 strategy * time \quad \text{Eq. (1)}$$

where time was incorporated as a continuous variable, was constructed for the purpose of comparing the utility trajectory over time between the 2 groups, adjusting for progression states (pre-progression and post-progression). Progression status was a binary variable defining whether the disease progressed (progression status =1) or not (progression status=0) after treatment. Strategy referred to the SABR + SoC or SoC.

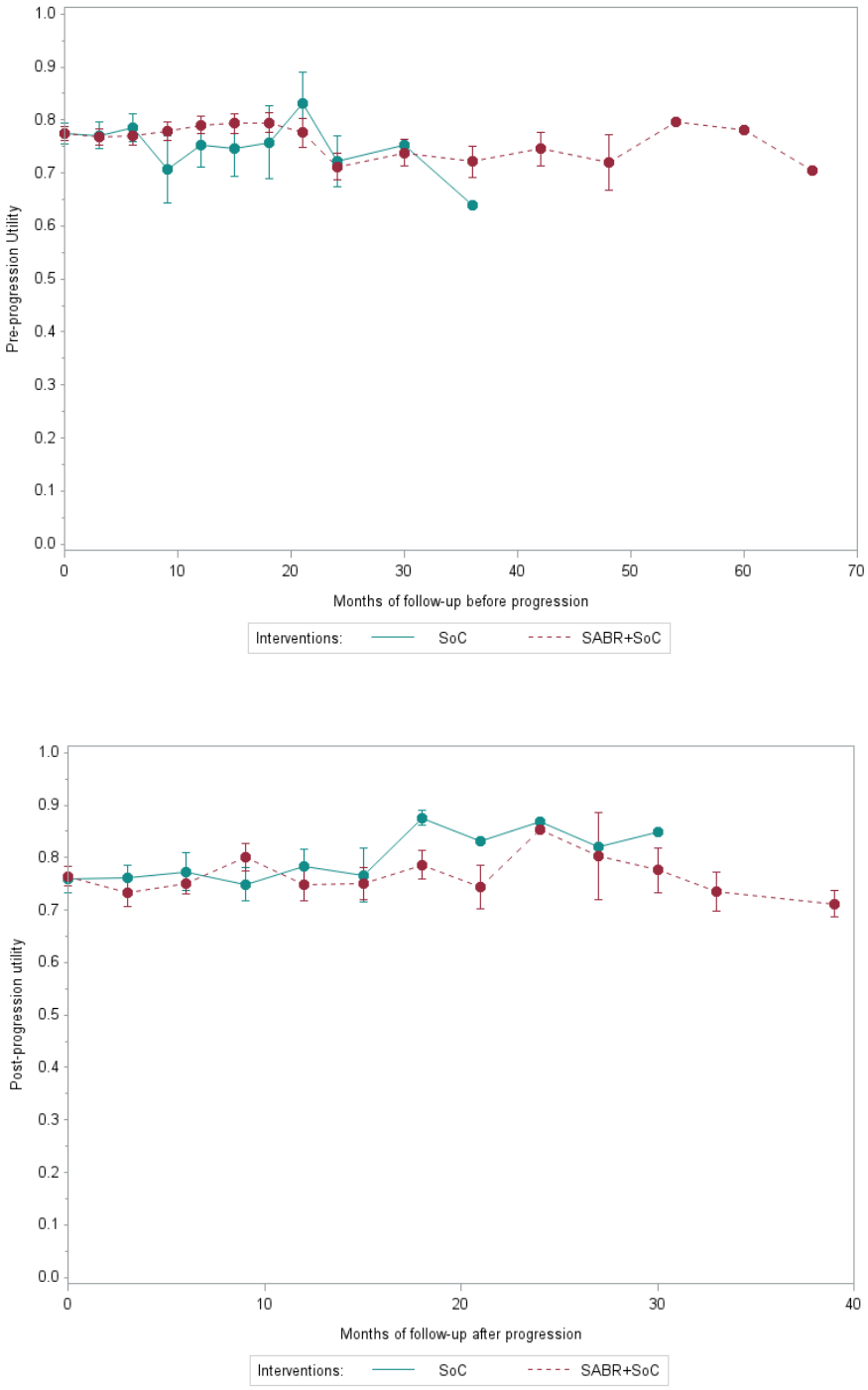


Figure 4. Utilities trend of 2 strategies before and after progression

3.2.4 Estimating the disutility

The disutility associated with the grade 2 or higher (more severe) fatigue, dyspnea and pain among non-small cell lung cancer patients were identified from published literature. We assumed that these utilities, although calculated for NSCLC patients, would be consistent among all patients with oligometastatic cancers, independent of primary tumour type.

The proportion of grade 2 or higher treatment-related adverse effects (AEs) in the SABR-COMET trial were significantly different among treatment groups. There were 3 out of 33 in SoC arm versus 19 out of 66 in SABR+ SoC arm, (9% vs. 29%, respectively, p= 0.026). Therefore, we considered it meaningful to modeling the dis-utility associated with grade 2 or higher adverse events. Given that most of the AEs were non-severe and of a short duration, the disutilities of AEs could not be reliably ascertained from individual patient data. Therefore, relevant disutilities were obtained based on a review of the available literature, as well as the Tufts Cost-Effectiveness Analysis Registry [62]. Limited by the availability of source data, we did not differentiate the disutility between grade 2 and grade 3 AEs (dyspnea, fatigue, pain) and conservative estimations (i.e. worse disutility for AEs, favouring SoC) were used whenever assumptions were required. The frequency, onset and duration of treatment-related AEs were obtained from the SABR-COMET trial. Given most patients experienced various AEs for less than 3 months, we conservatively assumed that adverse events lasted for 1 cycle (3 months), and that QALYs were calculated using the formula as listed:

$$\sum(proportion\ of\ patients\ with\ AE\ *\ disutility\ *\ length\ of\ AE) \qquad \text{Eq. (2)}$$

3.3 Deriving Costs

3.3.1 Total direct cost

Direct costs were estimated from the Canadian health care system perspective. Indirect costs were not included in this study. Cancer-specific total direct medical costs included chemotherapy, RT, inpatient hospitalization, same-day surgery, physician services, home and community care, diagnostic tests and out-patient prescription drugs, and these were

obtained from published research. The costs of outpatient drugs for patient younger than 65, emergency department visits and ambulatory care were not included. These costs were derived from linked cancer registry and administrative data in Ontario using standardized costing method reported by de Oliveira et al. [43]. We divided the total direct medical cost into three categories, which were RT cost, chemotherapy cost, and base care cost (the rest) to model each of the three costs separately, shown in the equation (3) below.

$$Total\ direct\ cost = Base\ care\ costs + Chemotherapy\ costs + RT\ costs \quad \text{Eq. (3)}$$

There were several reasons to model these costs separately. First, the main driver of the difference in cost between the two strategies is the cost of RT and SABR. SABR cost is not captured in the published costing studies, as it is applied to the new indication (oligometastases) in this setting. Second, cost of chemotherapy and other conventional RT were highly related to the use of SABR. As the SABR-COMET authors predicted that SABR was associated with less use of chemotherapy and other palliative RT due to delaying cancer progression. Third, cost for different categories of therapy have different occurrence and accumulation pattern. RT resulted in one-time cost for each health states, while chemotherapy and base care costs are repetitively charged and accumulated in each Markov model cycle. Therefore, the three costs were weighted by different proportion of users among each type of cancer, between arms (SABR+ SoC vs SoC) and health states (pre-progression vs post-progression), adjusted for different rate of cost increase, and assigned differently within the model.

Another reason that cost was modeled as different categories is that the expenditure on RT and chemotherapy has increased at different rate over years according to a population-based study [41]. This cost increase is associated with the availability of expensive new treatments, the application of therapies to more treatment indications, as well as the additional expenditure on supporting care due to extended survival over time. We use the estimated annual percent cost increase from the published literature to account for the potential cost increase when we adjusted the source data, representing a lower cost in 2005 [43], to a higher cost in 2012 when SABR-COMET trial was initiated.

All costs were adjusted to 2018 CAD using the consumer price index [63]. Although the price charged for goods increased overtime, the relative price remained the same. All costs were converted to 2018 CAD so that cost data from various sources could be standardized. The annual average costs were divided by 4 to obtain average quarterly costs, which were modeled and accumulated every cycle.

3.3.2 Base care costs

The base care costs were further split into two parts, based on different time-periods, base terminal care cost (within last 12 months of life) and base continue care cost (prior to the last 12 months of life). Cancer costs were not calculated separately for the last three months of life, as previous studies suggested that they do not significantly differ from costs in the last 4 to 12 months of life [64]. The base terminal care costs were calculated using equation (4). We extracted the annual total direct terminal care cost, terminal phase chemotherapy cost of and RT cost from the population-based costing study by de Oliveira et al. who reported the detailed terminal care costs for metastatic breast, colorectal, lung and prostate and other type of cancers [43].

$$Base\ terminal\ care\ cost = Total\ direct\ terminal\ care\ cost - Chemotherapy\ cost - RT\ cost \quad \text{Eq. (4)}$$

This study also provided the cancer-specific total direct continuing care cost. However, the cancer-specific annual chemotherapy cost and RT cost for continuing care were not available in this study. We therefore estimated the base continuing cost using equation (5), in which the proportion of chemotherapy cost and proportion of RT cost were derived from a separate study [44]. This study was performed by the same research group within the same time period, estimating the cancer care cost among the same population, and according to which, chemotherapy and RT costs accounts for 9% and 7% of the direct continuing care cost for cancer patients survived beyond one year, respectively.

$$Base\ continuing\ care\ cost = Total\ direct\ continuing\ care\ cost - (Proportion\ of\ chemotherapy\ cost + Proportion\ of\ RT\ cost) * Total\ direct\ continuing\ care\ cost \quad \text{Eq. (5)}$$

3.3.3 Chemotherapy costs

In this study, we intend to incorporate and model the chemotherapy costs for stage IV metastatic breast, colorectal, lung and prostate and other type of cancers. However, we were not able to directly identify the costs from published literature. Based on the available data sources we considered the chemotherapy cost during terminal care phase (within last 12 months of life), from the population-based costing study by de Oliveira et al. mostly resembled the potential cancer-specific chemotherapy cost for our patients population [43]. We subsequently identified the proportion of chemotherapy recipients, cancer patients who actually received chemotherapy, from a study done by the same group using similar approach [64]. These proportions, which were cancer-specific, were utilized to derive the cancer-specific average annual costs per chemotherapy recipient from the estimated the average annual costs per cancer patients. Finally, we calculated the weighted average of the cancer-specific average annual costs per chemotherapy recipient by adjusting cancer type according to SABR-COMET trial to reflect the clinical scenario for patients with stage IV cancer.

3.3.4 Radiotherapy costs

Radiotherapy costs were estimated according to the activity-based costing method used by Yong et al. [45]. The unit cost of each activity and the number of units required by SABR and palliative RT were identified from published studies [45]. SABR and palliative RT costs for treating each of metastases were derived from Ontario intensity-modulated radiation therapy (IMRT) and 3-dimensional conformal radiotherapy (3D-CRT) activity-based costing data, respectively.

The RT costs consist of 3 major resources: process costs, clinical infrastructure costs and overhead. The process costs include staff time and consumables. The clinical infrastructure costs account for the capital of acquisition, construction and maintenance as well as the operating cost. Overhead refers to the costs of supporting infrastructures required for maintaining the daily function of the program.

Table 4 shows the modeled RT delivered within each intervention, during the SABR-COMET trial follow-up period. The RT cost per metastasis for both SABR+ SoC and

SoC strategy were calculated for both before and after progression. They were weighted by the number of treated metastasis per RT recipient and the proportion of RT delivered among patients. This allowed for estimation of the average cost of RT per patient in the SABR-COMET trial. In the SABR group, all patients were treated with upfront SABR to all sites of metastases, and they could receive further SABR or palliative RT in the event of cancer progression. Meanwhile, in the SoC group, patients were treated with palliative RT when necessary, either before or after progression. In the COMET trial, data regarding the receipt of palliative RT were missing for over half of patients who received this treatment in the SoC strategy. This data was completely collected in the SABR + SoC strategy. As we were unable to distinguish the receipt of palliative RT as either before progression or post-progression in the SoC strategy, the following two assumptions were made to calculate the cost of RT:

1. We assumed that in the SoC arm, 20% of palliative RT recipients were treated before progression, shortly after randomization, while the remaining proportion of palliative RT was received after progression. This estimate is based on observed trial data and clinical experience. This assumption was subjected to a wide range of range of 0 to 50% in sensitivity analysis, to test its impact on the cost-effectiveness of the 2 strategies. In contrast, in the SABR+ SoC strategy, SABR was the only form of RT delivered pre-progression, and in the event of progression, patients were allowed to receive either SABR or palliative RT. These data were available from the SABR-COMET trial and were modelled accordingly.

2. The frequency of receiving the post-progression palliative RT was assumed to be exponentially distributed over time for both strategies. Palliative RT served to relieve symptoms related to cancer progression. Thus, we considered that the highest probability of receiving the post-progression palliative RT appeared once cancer progressed, and the probability of its use decreased overtime. The timing of receiving post-progression palliative RT was only available for 14 patients, of whom nine (64%) patients were treated immediately within the 3 months (the first Markov cycle) after cancer progression. Based on the available data on timing of palliative RT administration within the SABR-COMET trial, the probability of receiving post-progression RT over time can

be best described as an exponential distribution, with λ =1 under the base case scenario. As the cumulative distribution function was F(t)=$1 - e^{-\lambda t} = 1 - e^{-t}$, t= number of cycles (3 months) in post-progression health state. This distribution indicated that 63% of palliative RT happened within the first Markov cycle of post-progression health state, and it matched with the observed pattern in the clinical trial. We tested λ under a Gamma distribution with a standard deviation of 0.1 via probabilistic sensitivity analysis. In this way, the cost of post-progression palliative RT can be discounted as:

$$\begin{aligned} \textit{Present Value} &= \textit{palliative RT cost} * \sum_{t=1}^{10} \frac{[F(t)-F(t-1)]}{(1+r)^{t+n}} \\ &= \textit{palliative RT cost} * \sum_{t=1}^{10} \frac{e^{1-t}-e^{-t}}{(1+r)^{t+n}} \end{aligned} \qquad \text{Eq. (6)}$$

where n refers to number if cycles varied from 0 to 10.

Table 4. Summary of RT of two strategies stratified by cancer progression

	Pre-progression	Post-progression
SABR + SoC	SABR	SABR / Palliative RT †§
SoC	Palliative RT‡	Palliative RT§‡

Abbreviations: SABR, stereotactic ablative body radiotherapy; SOC, standard of care; RT, radiotherapy
‡ Assuming 20% of total palliative RT in SoC arm were received before progression, while the rest of 80% were post-progression RT.
† In SABR + SoC arm, patients with progressed disease can be treated with either SABR or palliative RT, if RT is needed.
§ The exponential distribution for post-progression palliative RT delivery in both arms were assumed.

3.3.5 Cost for managing adverse events

We also derived the cost of managing adverse events including fatigue, pain and dyspnea. The price of drugs were identified from the database "the electronic version of the Ontario Drug Benefit Formulary / Comparative Drug Index (Formulary / CDI)" [65]. The dispensing fee charged by the pharmacists for filling prescriptions was available at Ontario Ministry of Health and Long-Term Care [66]. The cost of managing AE were obtained by using information on the types of medication, dosage, duration, unit drug price and pharmacy dispensing fee. According to the trial data, the median time of onset was at cycle 1 for pain, cycle 3 for dyspnea. AEs were with a median length of 1 cycle,

and they were discounted according to the start time. The total cost was discounted for the time of AE start at an annual discount rate of 1.5%. There was no treatment for fatigue, therefore AE-related costs were calculated primarily from managing dyspnea and pain.

3.4 Deriving transition probabilities and other parameters

The transition probabilities were derived using the individual-level patient data from the SABR-COMET trial. We performed parametric survival analysis with Weibull distribution via the SAS LIFEREG procedure to obtain the survival function S(t). The Weibull model was chosen in our study for 2 reasons:

1. The survival function is expressed in a simple form as equation (7), with only three parameters including intercept (β_0), coefficient of intervention (β_1) and shape ($1/\sigma$).

$$S(t) = \exp\{-(te^{-\beta_0-\beta_1 x_1})^{\frac{1}{\sigma}}\} \quad \text{Eq. (7)}$$

2. It is the only model that belongs to both the accelerated failure time (AFT) and proportional hazard model categories. The hazard ratio (HR) in proportional hazard model has been widely used in clinical research and can be interpreted intuitively as the immediate relative risk of one group as compared to the other group over time. When we transform the model coefficient properly, the relative hazard ratio between two strategies can be obtained as HR=$e^{(-\beta_1/\sigma)}$ [67]. We use the HR to link the transition probability for the same health states between the two comparison groups. In this way, the proportional hazard assumption can be tested in sensitivity analysis to see the impact of HR on the calculated ICER. The transition probability in a 3-month cycle of each health state for SoC strategy was estimated as

$$p_{SoC} = \frac{S(t) - S(t+1)}{S(t)} \quad \text{Eq. (8)}$$

and the transition probabilities of the same health states for SABR strategy were represented by transition probability of SoC strategy and HR:

$$p_{SABR} = 1 - exp\,[HR * ln(1 - p_{SoC})] \quad \text{Eq. (9)}$$

The transition probabilities were derived from the 5-year follow-up data in SABR-COMET trial via Weibull survival analysis. A lifetime horizon was then extrapolated based on the 5-year trend of the model, by increasing the number of Markov cycles until the whole cohort was absorbed by any of the 3 death-related health states. In our model, twenty years (80 cycles) was used to represent lifetime horizon as there was less than 0.1% cohort alive, by that time.

3.5 Model validation

We used R (version 3.5.1) to overlay the model predictions on the Kaplan-Meier curves for OS and PFS generated using the individual-level patient data from the SABR-COMET trial and digitized from the published literatures for internal and external validation, respectively.

3.5.1 Internal validation

The purpose of internal validation was to confirm if the survival and progression pattern of the real cohort in the SABR-COMET trial were well predicted by the Markov model simulated cohort. Both the overall survival and the progression-free survival curves obtained by the model were visually and numerically compared with the Kaplan-Meier curves generated using the individual-level data from the trial.

3.5.2 External validation

The purpose of the external validation was to assess if the model simulated survival and progression patterns consistent with external data sources of similar patients with oligometastatic cancer. We searched literature that reported the long-term survival outcomes of SABR-treated oligometastatic lung, prostate, colorectal and breast cancers, as these comprised the majority of primary tumour types within SABR-COMET. We identified four eligible studies [18, 68-70]. Both overall survival and progression-free survival were validated by visually comparing the published survival curves with the model output. External validation was only performed for the SABR group, as outcomes

on SoC management of oligometastatic cancer patients are not well described in the literature.

As individual-level data were not available from these four studies, we used the reconstructing approach developed by Guyot et al. to map the individual-level survival data from digitized Kaplan-Meier curves for SABR-arm external validation [71]. The methods provided an accurate estimation of Kaplan-Meier data, especially the unavailable censoring information, based on the "number of events" and "probability of events" at every follow-up visit from the published Kaplan-Meier curves, by assuming a constant censoring rate during each interval (censoring is independent of the follow-up or non-informative censoring). The Engauge Digitizer software (digitizer.sourceforge.net) was used to digitize the Kaplan-Meier curves from the four published studies to extract the number of events and numbers at risk across the follow-up intervals.

3.6 Uncertainties and sensitivity analysis

Utilities and costs were obtained from various sources, and the majority of "probabilities/ proportions" and "other model parameters of interest" were derived from the SABR-COMET trial. Various sensitivity analyses were performed to evaluate the impact of parameter uncertainties as well as robustness of the predicted results. Both deterministic sensitivity analyses (DSA) and the probabilistic sensitivity analyses (PSA) were performed according to the methods recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Board [72].

In DSA, key parameters within the model were varied across plausible ranges, to determine their impact on model outputs. In 1-way sensitivity analyses, a single parameter is evaluated at a time. The aim in these exercises is to determine thresholds in which a parameter may influence the ICER value, beyond the willingness to pay threshold. We varied parameters, which were estimated from the individual-level data from the trial, such as Weibull parameters and proportions, within the 95% confidence intervals (CI) of the estimates. Costs were varied 30% above and below their baseline values. Utilities were varied by 0.1 below and above the baseline values to account for the potential variation in the mapping procedure.

In 2-way DSA, the interaction between the number of metastatic sites (determined the cost of SABR strategy) and the HR of PFS (indicated the comparative clinical efficacy of SABR versus SoC strategies) were evaluated. We intended to explore the minimal comparative clinical efficacy of SABR strategy required to maintain the cost-effectiveness of SABR when the cost of SABR strategy becomes higher. Although the SABR-COMET trial evaluated up to 5 metastases, we extended the upper limit of this range to 10 metastases. More generous ranges for selected parameters were used to facilitate interpretations of various clinical scenarios, for instance, the result of the 2-way SA was intended to generate hypothesis for the now accruing phase III SABR-COMET10 trial, which compares SABR vs. SoC in patients with 4-10 metastatic lesions (NCT03721341).

In PSA, all parameters within the model were varied simultaneously for multiple iterations to generate different ICER values. The baseline values, ranges, and probability distributions were assigned to these parameters.

Several probability distributions were applied in our model. Proportions, utilities and disutilities were properly defined with a beta distribution, as these types of parameters and beta distribution shared the same domain of 0 to 1. The annul discounting rate were defined with a uniform distribution, so that each value within the range of 0 to 0.03 can be sampled with an equal likelihood. Gamma distribution is widely used to describe the distribution of health care cost due to its flexibility to account for a positively skewed distribution from 0 to positive infinity. Therefore, in our model, each type of unit cost was defined by gamma distribution. We also used gamma distribution to define the distribution of different hazard ratios and relative risk of receiving chemotherapy use between two strategies. Normal distribution was used for each estimated Weibull parameter.

We assumed that the distributions of all of the model parameters are independent. Monte-Carlo simulation was used to randomly sample from the ranges of all selected parameters based on their distributions repetitively over a total of 5000 iterations. The ICER value was generated for each iteration. The distribution and range of the 5000 ICERs indicated

the robustness of our finding by quantifying the likelihood of the draw a conclusion that may be susceptible to the uncertainties. Therefore, PSA aimed to determine the percentage of iterations in which the SABR strategy would be considered cost-effective for WTP thresholds of $50,000/QALY gained and $100,000/QALY gained.

Chapter 4

4 Results

4.1 Health states utility and disutility

4.1.1 Mapping algorithms for predicting health utilities

A total of 7 mapping studies met the inclusion criteria were identified from the HERC database and relevant reference [34-38, 73, 74]. The 7 studies provided regression models converting the FACT-G scores to the health sates utilities. Of these, we excluded 3 studies, the first as it elicited utility values directly from patients rather than providing a generic preference-based utility [74] and the other 2 studies were excluded as the mapping involved only patients of Asian descent, which differ greatly from the race demographics of patients in the SABR-COMET trial [36, 73].

For the remaining 4 studies, 2 were performed by the same research group and provided the same mapping algorithm to convert FACT-G to EQ-5D based utilities. The patient characteristics, sample size and average FACT-G score of the rest of the 3 eligible studies were summarized and compared with the SABR-COMET trial in table 5.

Ultimately, the mapping study perform by Teckle et al. was the most relevant to patients from the SABR-COMET trial, with respect to baseline characteristics including country of origin, ECOG performance status, cancer type, sample source, and the FACT-G total scores. In addition, the mapping algorithm was internally validated in datasets with large samples sizes. The algorithm in this study employed the generalized linear model (GLM model 3), which utilizes FACT-G domain scores, primary cancer type and cancer stage as predictors of EQ-5D-based health utilities. The regression model is written as

$$\begin{aligned} log(Utility) = {} & 0.013 * PWB + 0.007 * FWB + 0.008 * EWB + 0.019 * Colorectal \\ & - 0.023 * Lung - 0.021 * stage2 + 0.025 * stage3 + \ 0.034 * stage4 \\ & - 0.867 \end{aligned}$$

PWB: physical well-being, FWB: functional well-being, EWB: emotional well-being, Colorectal: colorectal cancer patients, Lung: lung cancer patients, Stage: stage of disease;

Reference group: breast cancer, cancer stage 1.

This study developed mapping algorithms to obtain utilities based on EQ-5D and SF-6D based utilities. Of these we used the former, as EQ-5D is more widely applied.

Table 5. Comparison between the included mapping studies and the SABR-COMET trial

	Teckle 2013 [37]	Longworth 2014& Young 2015 [34, 38]	Meregaglia 2017 [35]	SABR-COMET trial 2018 [22]
Sample size				
Total	367	530	96	99
Development	184	530	79	NA
Demographic and clinical characteristics				
Country(s)	Canada	US	19 countries	Canada (80%), Netherlands (5%), Scotland (13%), Australia (2%)
ECOG PS score¶	PS=0: 35%, PS=1: 50%, PS=2: 11%, PS=3: 3%	PS=0: 23%, PS=1: 48.3%, PS=2: 24.7%, PS=3: 3.96%	PS=0-1: 81.2%, PS=2: 18.8%	0-1
Stage of tumour	Stage 1: 11%, Stage 2: 15%, Stage 3: 24%, Stage 4: 50%	Stage III or IV	Stage III or IV	Stage IV
Type of cancer	Breast:38%, Colorectal:31%, Lung:31%	11 types of cancers	Lung	Breast: 18.2%, Colorectal: 18.2%, Lung: 18.2%, Prostate 16.2%, Other: 29.3%
Age, mean (SD), years	58.7 (11.5)	59.01 (11.92)	61.1 (8.7)	66.9 (11.1)
Gender	33% male	51.7% male	68.7% male	60% male
Sample source	consented patients from Vancouver cancer clinic	1 US respondent data set	2 RCTs	A phase II RCT
Descriptive statistics for FACT-G Total Score				
Mean (SD) Median (Range)	78.87 (15.47) 81(36, 107)	77.92 (15.16) 79 (33, 108)	64.9 (14.2) (18, 95) §	81 (17.3) 83 (24,108) ‡

¶ good performance status (Eastern Cooperative Oncology Group score.
‡ The FACT-G score is estimated among each follow-up of each individual.
§ Only mean, SD, range, rather than median, of the FACT-G total score were reported in this study.

4.1.2 Estimating the average health utilities

The pre-progression and post-progression utilities were estimated using the method mentioned in section 3.2.3. According to the result, we cannot reject the null hypothesis of β_1(P=0.999) and β_4(P=0.44) equal to 0. Therefore, the utilities did not differ significantly between the 2 interventions. We then regress the utility on time and adjusted for progression status,

$$Utility = \beta_0 + \beta_1 time + \beta_2 progression\ status.$$

As follow-up time only had a very small effect on the utility (β_1 = - 0.0003, p =0.6). The model was simplified to:

$$Utility = -0.029\ progression\ status + 0.772$$

to represent the overall mean health utility of the general patients, regardless of the intervention group for pre-progression and post-progression states.

The mean pre-progression and post-progression utilities calculated from the mapping algorithm at each follow-up visit are summarized in Table 6.

Table 6. Summary of health utilities

	Before progression	After progression	ΔUtility
Mean (p-value)	0.772 (p=0.0001)	0.743	-0.029 (p=0.0001)

Δutility: the mean utility difference due to disease progression.
Analysis performed with linear mixed model

4.1.3 Adverse events, disutility and disutility-related QALY decrease

The treatment related adverse events (grade≥2 toxicities) in the SABR-COMET trial and the estimated disutilities related QALY decrements are summarized in Table 7. The disutilities as a result of severe toxicities (grade≥3) related disutilities were identified from two previous studies [75, 76]. Both studies elicited the disutility using the standard gamble method from the general public, reflecting the societal value placed on the burden

of severe symptoms (grade≥ 3 toxicities such as fatigue, pain and dyspnea) and disease progression states (progressive or stable) of non-small cell lung cancer.

Grade 2 or higher toxicities were considered clinically meaningful and the risk was significantly higher risk in the SABR group, and therefore was accounted for in the model. As a conservative assumption, all of these were assigned the utility decrement that was calculated for more severe (grade 3 or higher) toxicities within the source studies. This would bias the incremental utility towards null, given the higher incidence of less severe toxicities in the SABR group. We observed that, on average, most AEs lasted for one follow-up interval within the trial, therefore, we assumed that any disutility would last for 1 full cycle (i.e. 3 months) within the model. Among the three types of most frequent AEs, fatigue mainly started immediate after randomization, pain mostly occurred between 3th and 6th month, dyspnea was more frequently observed at the 9th month. The different onsets of the AEs were added in at the appropriate stage of the Markov model.

Table 7. Treatment-related toxicities and QALY decrease (disutility)

	SABR+ SoC (n=66)	SoC (n=33)	Disutility*
Pain	8 (12%)	0 (0%)	-0.069 [76]
Fatigue	4(6%)	3(9%)	-0.073 [75]
Dyspnea	2 (3%)	0 (0%)	-0.05 [76]
QALY	-0.0036¶	-0.0017§	

*Disutility associated with grade 3 or higher toxicities identified from published studies.
§ The disutility associated QALY decrease in SoC group. Fatigue was assumed starting at cycle 0 and last for 1 cycle (3 months), estimated as proportion of fatigue*disutility of fatigue*cycle length, cycle length =1/4 year.
¶ The disutility associated QALY decrease in SABR+ SoC group. Assumptions: Fatigue starts at cycle 0 and last for 1 cycle (3 months); pain starts at cycle 1 (3rd months) and last for 1 cycle (3 months); dyspnea starts at cycle 3 (9th months) and last for 1 cycle (3months). The QALY decrement were estimated based on the risk of each type of AE related to both strategies, the disutility related to each type of AE identified from published literature, and the starting time and lasting time of these AEs.

4.2 Cost

Costs were estimated from the Canadian health system perspective. The average direct costs of SABR+ SoC and SoC alone were estimated for oligometastatic cancer patients in the SABR-COMET trial. Our model assumed no death-related cost. Adding SABR to the SoC resulted in higher initial RT costs, but also resulted in a lower use of subsequent palliative RT (21 [64%] out of 33 patients in the SoC vs 13 [20%] out of 66 patients in

SABR+ SoC) and chemotherapy (16 [49%] of 33 patients in the SoC vs 20 [30%] of 66 patients in SABR + SoC group).

4.2.1 The cost of SABR versus palliative RT

The average costs of SABR for treating each metastasis was $8,378. In contrast, the average cost of palliative RT was $5, 736 in 2018 CAD (table 8).

Table 8. Summary of RT cost

	Unit cost* (range) [45]	**Units*** Mean (range) **Palliative RT** [45]	**SABR** [45]
Consultation			
Radiation oncologist	197.24 (per course) [77]	1	1
Nurse	126.91(per course)	1	1
CT simulation			
Therapist	94.34 (per course)	0.5x2	0.5x2
CT simulator	288.64(per course)	1	1
Immobilizer	15.72 (per course)	1	1
IT: patient management	79.74 (per course)	1	1
Dosimetry			
Therapist	94.34 (per hour)	0.5	2.5 (1.5, 3.5)
Planning system	203.28 (per hour)	0.5	2.5 (1.5, 3.5)
Radiation oncologist			
Palliative RT	725.29 (per course) [77]	1	
SABR	855.29 (per course) [77]		1
IT: patient management	79.74 (per course)	1	1
Physic quality assurance			
Physicist	131.40 (per hour)	0.15	2 (1, 3)
Physics associates	96.59 (per hour)	-	0.75x2
Specialized QA equipment	64.02 (per course)	-	1
Planning system	203.28 (per hour)	0.15	2 (1, 3)
IT: patient management	79.74 (per course)	1	1
Preparation and delivery and review			
Therapist: Pre-treatment	94.34 (per hour)	3.08	3.08
Therapist: On the unit	94.34 (per hour)	2.86x0.25x5	2.86x0.5x5
Linear accelerator	479.57 (per hour, per fraction)	0.25x5	0.5x5
Radiation oncologist	81.89 (per course) [77]	1	2
Nurse	126.91 (per course)	1	1
IS: patient management	79.74 (per course)	1	1

(continuous from previous page)

	Unit cost* (range) [45]	**Units*** Mean (range) **Palliative RT** [45]	**SABR** [45]
IS: record or verify [45]	55.03 (per hour)	0.25x5	0.5x5
Treatment time per fraction		0.25	0.5
Number of fractions		5 (1, 15)	5 (1, 8)
Number of review visits		1	2
Peer review quality assurance	39.19 (per course) (27.53, 80.55) **[78]**	1	1
Supporting infrastructure	2,225.99 (per course)	1	1
TOTAL COST (2018 CAD)		**5736.15**	**8377.57**

Abbreviation: IS, information system; CT, computation topography; SABR, stereotactic ablative body radiotherapy; RT, radiotherapy.
Activity process were adapted from Yong et al. [45]. *Unit costs and units were adapted from Yong et al. [45], otherwise clarified varied +/-30% for sensitivity analysis. Physician billings are based on 2018 fee schedule [77]. The physician base funding is allocated to each visit per method described by Yong et al. [45].
Cost is adjusted to 2018 Canadian dollars.

4.2.2 The chemotherapy costs among two strategies

We calculated the mean chemotherapy costs by weighing the annual average cost of chemotherapy per recipient in the SABR-COMET trial (Table 9) by proportion of recipients among each group (48.48% in SABR + SoC and 30.30% in SoC group). The mean annual chemotherapy costs for stage IV cancer patients were used to estimate the unit cost of chemotherapy for treating oligometastatic cancer. The annual mean cost of chemotherapy was $6,307 in the SABR+ SoC group vs $10,091 in the SoC group.

Table 9. Annual average chemotherapy cost of the SABR-COMET trial

Cancer type	Mean cost of chemotherapy in 2005 among cancer patients (2018 CAD)	Mean cost of chemotherapy in 2012 among cancer patients (2018 CAD)	Mean cost per chemotherapy recipient (2018 CAD)	Proportion of each cancer type in SABR-COMET trial (2018 CAD)	Annual mean cost of chemotherapy per recipient in SABR-COMET trial (2018 CAD)
Breast	4,981†	11,527§	11,527/0.73=15,750¶	0.182‡	
Colorectal	5,112†	11,831 §	11,831/0.43=27,826¶	0.182‡	
Lung	3,425†	7,927§	7,927/0.30=26,004¶	0.182‡	20,813
Prostate	1,448†	3,350§	3,350/0.54=6,186¶	0.162‡	
Other	4,352†	10,071§	10,071/0.41=24,450¶	0.293‡	

Chemotherapy cost are in 2018 Canadian dollars.
†Average cost of terminal cancer care (12 months before death) for all cancer patients by de Oliveira et al. [43], assumed to reflect the cost of 2005.
§Adjusted for 7-year cost increase with an annual percentage growth rate of 16.62% [41]. The calculation is demonstrated in Table 10.
¶Average cost of chemotherapy among users: average chemotherapy cost among overall cancer patients weighted by proportion of chemotherapy users among all cancer patients in last 12-4 months before death [64].
‡Proportion of each cancer type in SABR-COMET trial [22].

As the expenditure of cancer treatment increased over time, and the source cost were calculated in 2005 dollars, we adjusted the source cost for a 7-year cost growth to estimate the real costs in SABR-COMET which was initiated in 2012. This was performed according to a previous a population-based costing study, in which the Ontario patient-level costs of cancer care (chemotherapy, RT etc.) over years (including 2005 and 2012) were reported [41].

4.2.3 The phase dependent base cost

The annual average base cost of the terminal care (Table 10) versus continuing care (Table 11) were $94,769 and $14,510, respectively. The base costs were consistent between two strategies and consisted of costs from in-patient hospitalization, same-day surgery, physician services, diagnostics tests, out-patient prescription drugs and community care. In the Markov model, all patients in the trial have contributed to the terminal care base cost while only patients who survived for more than 12 months contributed to the continuing care base cost.

Table 10. Annual average terminal care base cost of the SABR-COMET trial

	Total	RT cost	Chemotherapy cost	Base cost in SABR-COMET trial	Proportion of each cancer type in SABR-COMET trial	Annual average base cost terminal care
	(2018 CAD)	(2018 CAD)	(2018 CAD)	(2018 CAD)	(2018 CAD)	(2018 CAD)
Breast	90,503†§	2,372†§	11,527†§	76,604¶	0.182‡	94,760
Colorectal	108,924†§	1,071†§	11,831†§	96,022¶	0.182‡	
Lung	116,868†§	4,122†§	7,927†§	104,819¶	0.182‡	
Prostate	88,238†§	1,404†§	3,350†§	83,485¶	0.162‡	
Other	117,863†§	2,570†§	10,071†§	105,223¶	0.293‡	

Costs are in 2018 CAD.
Terminal care: the cancer management within last 12 month before death.
¶Base cost = total direct cost – (RT cost + chemotherapy cost).
† account for inflation
§ adjusted for a 7-year cost increase with an annual percentage growth rate of 8.56%, 12.73% and 16.62% for the total cost, RT cost and chemotherapy cost, respectively [41].
‡ Proportion of each cancer type in SABR-COMET trial [22].

Table 11. Annual average continuing care base cost of the SABR-COMET trial

	Total (2018 CAD)	RT cost (2018 CAD)	Chemotherapy cost (2018 CAD)	Base cost in SABR-COMET trial (2018 CAD)	Proportion of each cancer type in SABR-COMET trial (2018 CAD)	Annual average base cost continuing care (2018 CAD)
Breast	18,040[†§]	2,085[*†§]	2,115[*†§]	13,840[¶]	0.182[‡]	14,510
Colorectal	23,322[†§]	2,696[*†§]	2,734[*†§]	17,892[¶]	0.182[‡]	
Lung	20,133[†§]	2,327[*†§]	2,360[*†§]	15,446[¶]	0.182[‡]	
Prostate	16,972[†§]	1,962[*†§]	1,990[*†§]	13,021	0.162[‡]	
Other	17,030[†§]	1,968[*†§]	1,997[*†§]	13,066[¶]	0.293[‡]	

Costs are in 2018 CAD.
Continuing care: the cancer management between the initial phase (the 6 months after diagnosis) to terminal phase (last 12 month before death).
¶Base cost = total direct cost – (RT cost + chemotherapy cost).
† account for inflation
§ adjusted for a 7-year cost increase with an annual percentage growth rate of 8.56%, 12.73% and 16.62% for the total cost, RT cost and chemotherapy cost, respectively [41].
‡ Proportion of each cancer type in SABR-COMET trial [22].
*RT cost and chemotherapy cost account for 7% and 9% of total direct cost for continuing care [44].

4.2.4 The cost for adverse effect management

The costs of drugs for managing the treatment related toxicities are summarized in Table 12. The dispensing fee charged by the pharmacists for filling prescriptions is $8.83 (2014 CAD), which equals to $9.34 in 2018 CAD.

Table 12. Cost of adverse effect management

	Duration	Management	Unit cost	Total cost
G2 pain	3 months	Acetaminophen 650mg QID x 90 days	Apo-Acetaminophen Caplets 325mg $0.0285 Dispensing fee $9.34	29.86
G3 pain	3 months	Additional Hydromorphone 2mg Q4H x 90 days	Dilaudid 2mg Tab $0.1417 Dispensing fee $ 9.34	85.86
G2 dyspnea	3 months	Salbutamol puffer 2 puff QID x90 days	Ventolin HFA 100mcg/Metered Dose Inh-200 dose $6.00 Dispensing fee $ 9.34	30.94
G3 dyspnea	3 months	Additional Hydromorphone 0.5mg Q4H x 90 days Prednisone 50 mg OD x2wk, 40mg OD x2wk,30mg OD x2wk, 20mg OD x2wk, 10mg OD x2wk, 5mg OD x2wk	Dilaudid 1mg Tab $0.0959 Apo-Prednisone 50mg Tab $0.1735 Apo-Prednisone 5mg Tab $0.022 Dispensing fee $ 9.34 x 2	53.47
Fatigue	3 months	no pharmacological intervention	-	0

Cost are in 2018 Canadian dollars.
Abbreviation: G2, Grade 2 toxicities; G3, Grade 3 toxicities.

4.3 Base case cost-effectiveness analysis

4.3.1 Internal and external validation of the Markov model

We numerically compared the total number of deaths from any cause as well as the number of survivals without progression at the 27th month (Table 13) and 24th month (Table 14). The two time points were close to the median time of follow-up of 25 months in the SABR-COMET trial.

According to the model output, there were 22 versus 17 deaths in the SABR versus SoC strategy. This result matched well with the findings of the trial, in which 21 and 12 deaths were observed in the SABR arm and Soc arm, respectively (Table 13). The similar progression-free survival was also observed in the comparison of model output and trial report. There were 28 and 5 patients remained progression-free survival in the trial after 27 months of follow-up in the SABR arm and SoC, respectively, while our model reported 20 with SABR strategy and 3 with SoC strategy within progression-free survival states accordingly.

Table 13. Comparing number of events between trial and model at the 27th month

	Death from any cause		**PFS**	
	Trial	Model	Trial	Model
SABR (n=66)	21	22	28	20
SoC (n=33)	12	17	5	3

Abbreviation: SABR: stereotactic ablative radiation therapy, SoC: standard of care. PFS: progression-free survival.

At the 24th month, there were 18 and 11 deaths in SABR arm and SoC arm, respectively, which corresponded to the model simulated results showing that 19 and 15 deaths in SABR and SoC strategy, respectively (Table 14). The good model fit was also demonstrated by comparing the trial reported PFS with modeled PFS. There were 28 and 6 patients remained progression-free survival in the trial after 27 months of follow-up in

the SABR arm and SoC, respectively, while our model reported 22 with SABR strategy and 3 with SoC strategy within progression-free survival states accordingly.

Table 14. Comparing number of events between trial and model at the 24th month

	Death from any cause		PFS	
	Trial	Model	Trial	Model
SABR (n=66)	18	19	28	22
SoC (n=33)	11	15	6	3

Abbreviation: SABR: stereotactic ablative radiation therapy, SoC: standard of care. PFS: progression-free survival.

Internal validation of the model outputs was performed by overlaying the model simulated survival curves with Kaplan-Meier curves from SABR-COMET. This is depicted in Figure 5. The modeled overall survival and progression-free survival patterns fit well with the trial-based survival patterns based on visual comparison, suggesting internal validity of our model.

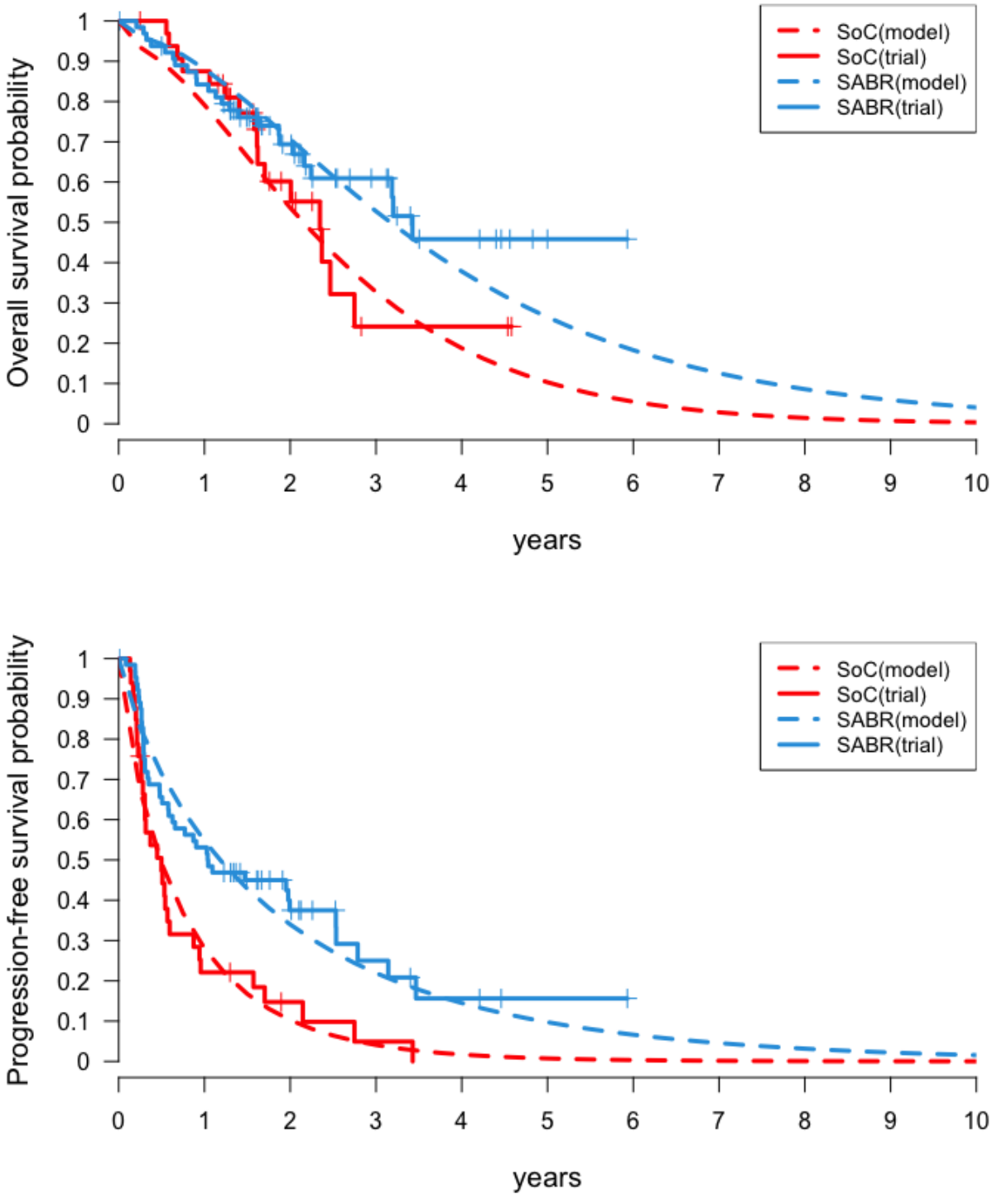


Figure 5. Interval validation of the overall survival (OS) and progression-free survival (PFS)

The results of external validation are presented in Figure 6. Studies used for external comparison are summarized in Table 15. A total of 4 studies exploring the effectiveness of radical RT on the survival of patients with oligometastatic breast, colorectal, lung and prostate cancer were identified [18, 68-70]. From these studies, patients with breast and prostate oligometastatic cancers had the best prognosis. Meanwhile, oligometastatic lung cancer patients had higher rates of early cancer progression and inferior survival. As our hypothetical cohort consisted of a mixed group of primary tumors, predicted progression and survival was within the range of these outcomes.

Table 15. Summary features of the four studies for external validation

	Trovo 2018 [70]	Filippi 2015 [68]	Lara 2018 [18]	Jereczek-Fossa 2012 [69]
Sample size	54	56	66	34
Population				
Age, years median (range)	55 (36, 83)	70 (44, 86)	70.5 (50, 90)	68.3 (57, 82)
Primary tumor	breast	colorectal	lung	prostate
Performance status (ECOG)	0 or 1	0 or 1	0 or 1	0 or 1
No. lesions (n, n%)	1 (27, 50%) 2 (19, 35%) 3 (6, 11%) 4 (1, 2%) 5 (1, 2%) mean 1.7	1 (26, 65%) 2 (10, 25%) 3-4 (4, 10%)	1(52, 79%) 2 (10, 15%) 3 (4, 6%) 4 (0, 0%)	34 patients and 38 lesions
SABR dose	30-36 Gy/3 fx, 85% 45 Gy/3 fx, 15%	26 Gy/1 fx, 68% 45 Gy/3 fx, 20%	48–52 Gy /4 fx, 30% 30–60 Gy/3 fx, 30% 30–40 Gy/5 fx, 14% 30–35 Gy/ 4-5 fx, 45%	30 Gy/5 fx, 56% 33 Gy/3 fx, 35% 36 gy/3 fx, 9%
Study design	Phase II multicentre prospective study	Prospective cohort	Retrospective cohort	Prospective cohort
Duration	2012 Jan-2015 Dec	2004-2014	2019-2015	2007 May-2009 Dec

Abbreviation: SABR: stereotactic ablative radiation therapy; fx: fractions; ECOG: Eastern Cooperative Oncology Group.

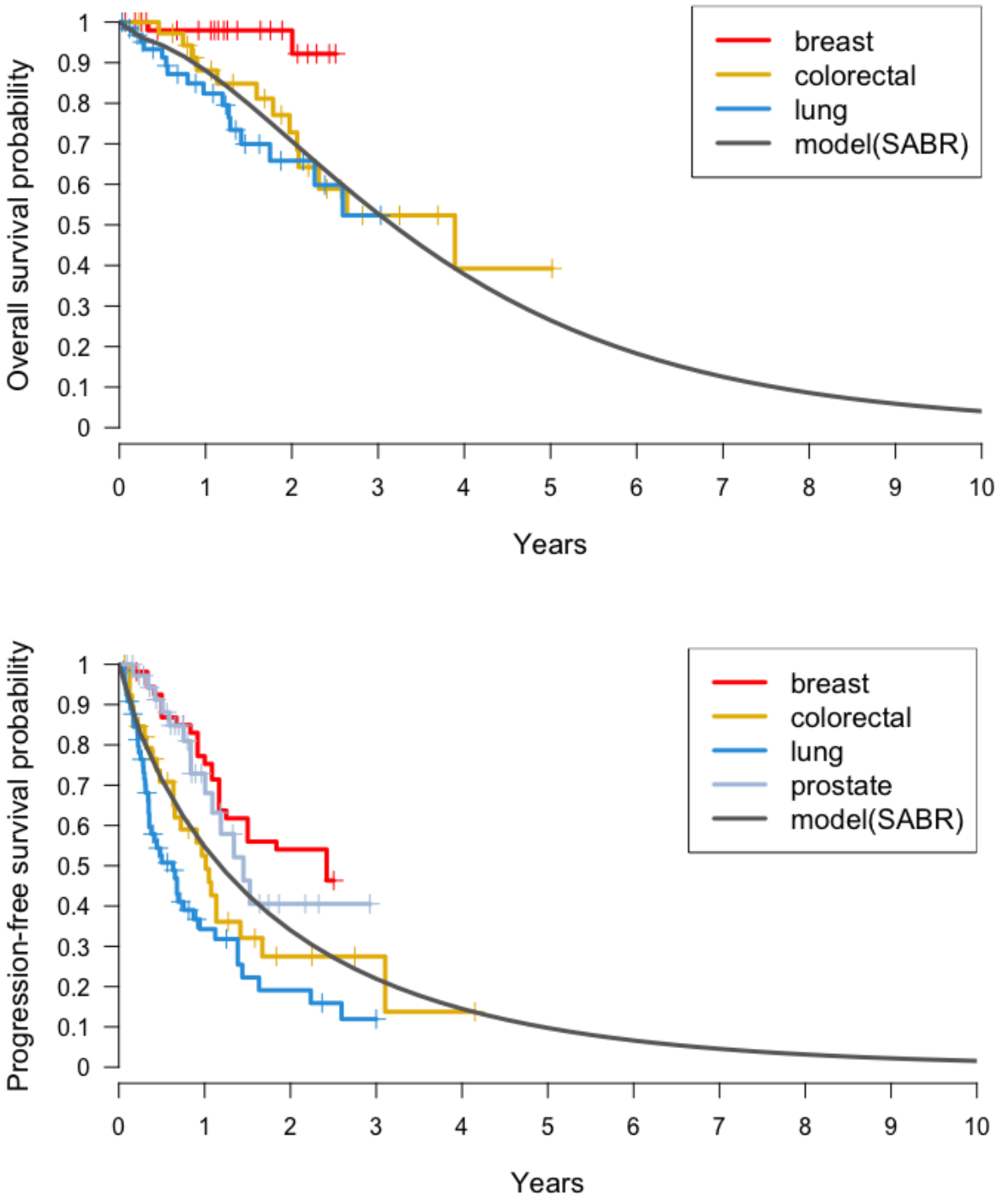


Figure 6. External validation of the overall survival and progression-free survival

Studies reported overall survival and progression free survival curves for external validation were identified from published literature for the different types of cancer, including breast[70], colorectal[68] and lung [18]. For prostate cancer studies, however, overall survival were not commonly reported, and therefore only progression-free survival was externally validated [69].

4.3.2 Summary of parameters and uncertainties

The model parameters and range of uncertainties are summarized in Table 16. In this study, model parameters consist of costs, utilities and disutilities, transition probabilities, annual discount rate and other parameters that describes the proportion of population or events. Listed below are all parameters, except for the transition probabilities, and their values under base case scenario, potential ranges, sources and assumed distributions. Since our transition probabilities are time dependent, we plotted the cumulative probability of every health states over Markov cycles during a lifetime horizon (Figure 6).

Table 16. Model parameters and uncertainties

Variable	Value	Min	Max	Source	Distribution
Probability/proportion					
Grade 2 dyspnea in SABR arm	0.030	0.008	0.104	SABR-COMET	Beta
Grade 3 dyspnea in SABR arm	0.030	0.008	0.104	SABR-COMET	Beta
Grade 2 pain in SABR arm	0.091	0.042	0.185	SABR-COMET	Beta
Grade 3 pain in SABR arm	0.061	0.024	0.146	SABR-COMET	Beta
Grade 2-3 fatigue in SABR arm	0.076	0.033	0.165	SABR-COMET	Beta
Grade 2-3 fatigue in SOC arm	0.091	0.031	0.236	SABR-COMET	Beta
Grade 5 death in SABR arm	0.455	0.016	0.125	SABR-COMET	Beta
Palliative RT receipt in SOC arm	0.636	0.466	0.778	SABR-COMET	Beta
Palliative RT receipt in SABR arm[¶]	0.333	0.206	0.490	SABR-COMET	Beta
Post-progression SABR receipt in SABR arm[¶]	0.205	0.108	0.355	SABR-COMET	Beta
Pre-progression palliative RT receipt in SOC arm	0.2	0	0.5	Assumed	Beta
Chemotherapy use in SOC arm	0.485	0.308	0.665	SABR-COMET	Beta
Utility/disutility					
Pre-progression	0.772	0.672[*]	0.872[*]	SABR-COMET	Beta
Progression	-0.029	-0.180 [75][*]	0[*]	SABR-COMET	Beta
Dyspnea	-0.050	-0.074	-0.026	Doyle [76]	Beta
Pain	-0.069	-0.093	-0.045	Doyle [76]	Beta
Fatigue	-0.073	-0.110	-0.037	Nafees [75]	Beta
Cost					
SABR (per course)	8,378[‡]	5,238[‡]	12,384[‡]	Yong [45] Mutsaers [78]	Multi-parameters
Palliative RT (per course)	5,736[‡§]	4,421[‡§]	9,320[‡§]	Yong [45] Mutsaers [78]	Multi-parameters
Chemotherapy (per year)	20,813[‡§]	13,908[‡§]	28,363[‡§]	de Oliveira [41, 43] Pataky [64]	Multi-parameters
Base cost continuous care (per year)	14,510[‡§]	7,811[‡§]	22,902[‡§]	de Oliveira [41, 43, 44]	Multi-parameters

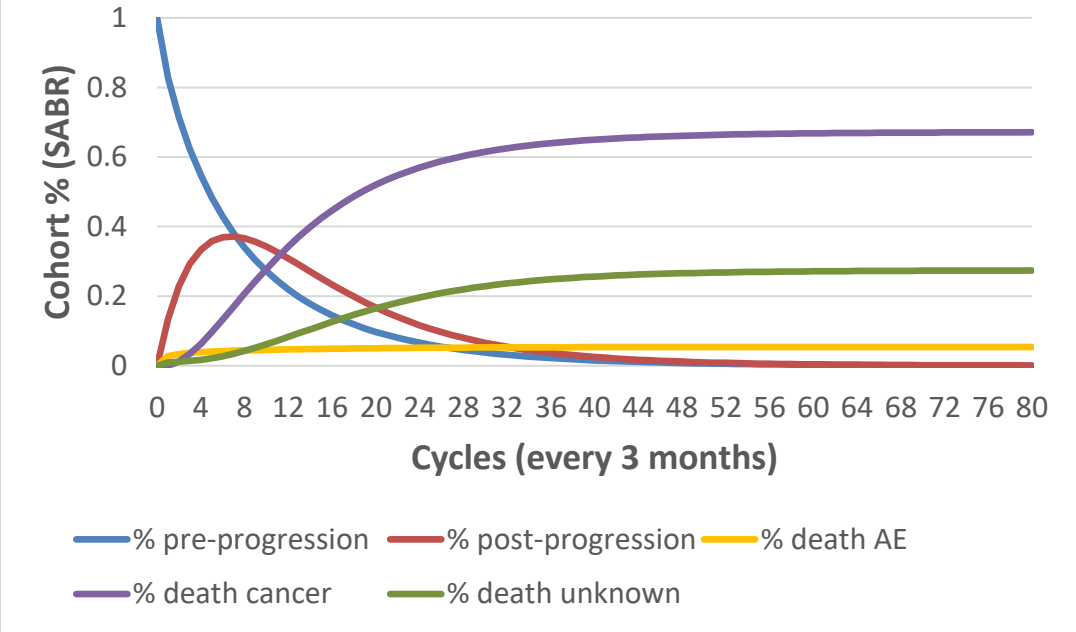
(continuous from previous page)

Variable	Value	Min	Max	Source	Distribution
Base cost terminal care (last 12 months)	94,760‡§	65,000‡§	125,643‡§	de Oliveira [41, 43]	Multi-parameters
Managing grade 2 dyspnea	29.86‡	20.90	38.82	MOHLTC [79, 80]	Gamma
Additional cost for managing grade 3 dyspnea	86.86‡	60.10	111.62	MOHLTC [79, 80]	Gamma
Managing grade 2 pain	30.94‡	21.66	40.22	MOHLTC [79, 80]	Gamma
Additional cost for managing grade 3 pain	53.47‡	37.43	69.52	MOHLTC [79, 80]	Gamma
Other parameters of interest					
No. pre-progression metastases/pt	2	1 (1.80)*	5 (2.20)*	SABR-COMET	Gamma
No. SABR-treated post-progression metastases/pt	1.75	1 (0.94)*	5 (2.56)*	SABR-COMET	Gamma
RR of chemotherapy use (SABR vs. SOC arm)	0.625	0.376	1.038	SABR-COMET	Gamma
HR: PFS (reference: SoC)	0.47	0.294†	0.758†	SABR-COMET	Gamma
No. palliative RT-treated metastases /pt	1.9	1 (1.53)*	4 (2.27)*	SABR-COMET	Gamma
HR: die of cancer progression (reference: SoC)	0.474	0.294†	0.758†	SABR-COMET	Gamma
Annual discount rate	0.15	0	0.03		Uniform

Abbreviations: SABR, stereotactic ablative body radiotherapy; SOC, standard of care; /pt, per patient; RR, relative risk; RT, radiotherapy; HR, hazard ratio; PFS, progression-free survival.
Range are selected based on 95% confidence interval estimate unless otherwise specified. Cost is adjusted to 2018 Canadian dollars. Source costs were varied by +/- 30%.
* Wider range selected by authors for deterministic sensitivity analysis to facilitate interpretation of various clinical scenario, while 95% confidence interval (presented in parenthesis) were used for probabilistic sensitivity analysis.
‡Calculated values, summary only. Sensitivity analysis performed at individual parameter levels.
§Adjusted cancer types based on SABR-COMET trial.
¶ Proportions were calculated among progressed cancer patients after initial treatment.

Figure 7 shows the proportion of the cohort distributed across the five health states over time, which was determined by the time-dependent transition probabilities. The curves that show the cohort percentage in pre-progression state depict the PFS patterns simulated by the model. As patients treated with SABR strategy achieved longer median PFS as compared to patients in the SoC strategy, the post-progression survival pattern altered accordingly, suggesting that the cohort percentage in post-progression state were mainly driven by cancer progression. The death due to AE happened in the SABR group as soon as the treatment started. Patients received SoC died earlier due to cancer progression and non-cancer reasons as compared to patients treated by SABR strategy. There were 67% vs 65 % cancer deaths in the SABR vs SoC in our model. The higher proportion of death from cancer in the SABR group may have resulted from the observational bias of the trial. SABR-COMET trial was open-labeled, and patients in the SABR group might have been more intensively followed as compared with patients in the SoC group. Therefore, patients who actually died from cancer in the control group (SoC) might more likely to be misclassified as death from non-cancer reasons, as compared to the intervention group

(SABR). In other words, the death from cancer might more likely to be captured and recorded in the SABR group. As we were modelling the clinical trial and extrapolate the 5-year survival patterns to a lifetime horizon (20 years), the consequence of the misclassification was amplified and resulted in a higher proportion of patient death from cancer in the SABR group.



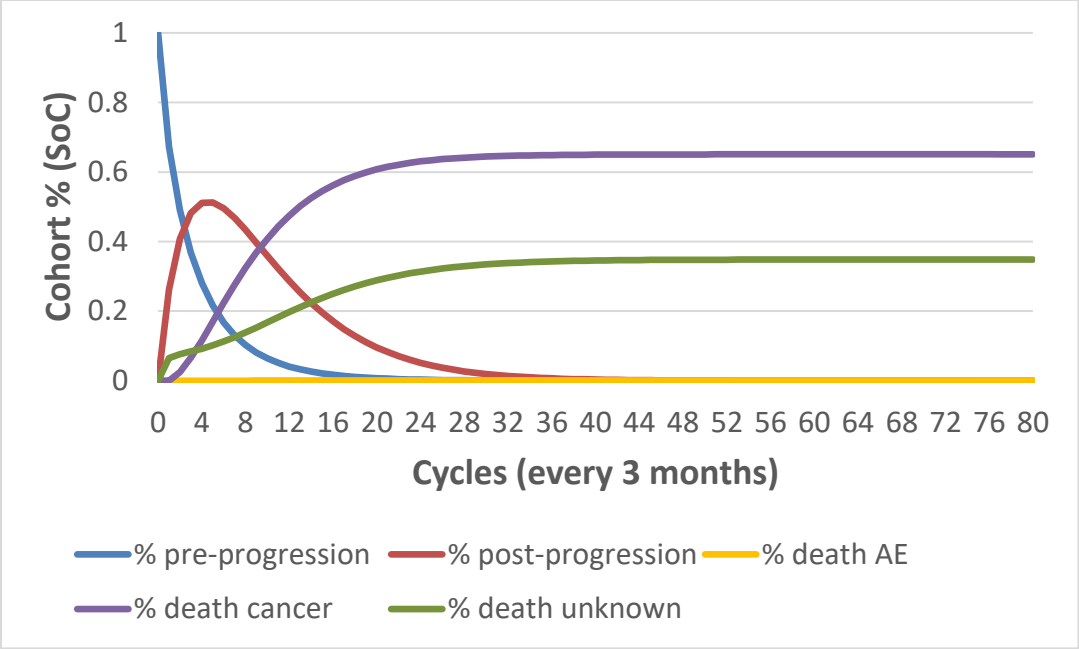


Figure 7. Markov states probabilities

4.3.3 Base case cost-effectiveness of SABR

The cumulative expected health benefit from the Canadian healthcare system's perspective over a lifetime horizon for SABR+ SoC was 2.78 QALY, at a cost of $169,693 (2018 CAD), while the cumulative expected health benefit of the SOC was 1.85 QALY at a cost of $ 135,452 (2018 CAD). Accordingly, the incremental cost-effectiveness ratio was $37,157/ QALY over a lifetime horizon. This base-case ICER was lower than the WTP threshold of $100,000/QALY. This result can be interpreted that SABR costs less than average required in health care system to exchange for 1 unit of QALY, and therefore the incremental cost can be justified by the health benefit gained. In sum, the combination of SABR with current standard of care was considered as cost-effective from the Canadian health care system perspective under the base-case scenario in which all conditions, except for the lifetime horizon, approaches to the clinical trial.

A cost-effectiveness analysis evaluating the incremental cost per unit additional life year (LY) saved was also performed. In base case scenario, SABR strategy saved 3.66 life years at a cost of $169,693 (2018 CAD), whereas SoC strategy required $135,452 (2018 CAD) to save 2.47 life years. Therefore, the calculated ICER which refers to incremental

cost per life year saved equals to $28,554/LY within a lifetime horizon. (Appendix E: ICER($/LY) of SABR+SoC versus SoC alone over time)

The ICER within the 5-year trial duration was $24,038/QALY (2018 CAD), which was lower than the $37,157/ QALY over a lifetime horizon, suggesting a potential bias towards the cost-effectiveness results if we had not extrapolated the model to a lifetime horizon. The ICER value over time is plotted in Figure 8.

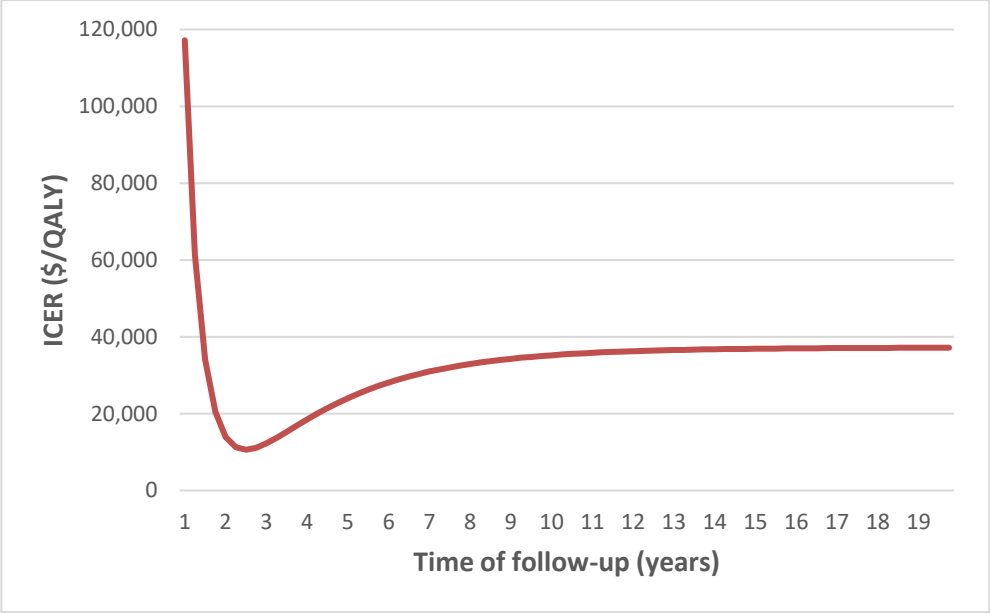


Figure 8. ICER of SABR+ SoC vs SoC alone over time

Since the health states utilities are the same for the 2 strategies, and the dis-utilities caused by adverse events have a minor effect on the QALYs (SABR+ SoC vs SoC: 0.0047 vs 0.0017). The incremental health benefit incurred was mainly due to the extend survival gained for patients receiving SABR. In addition, the rapid progression and death among patients receiving SoC alone resulted in significantly lower calculated QALYs as compared to the SABR-treated patients.

4.4 Sensitivity analysis

DSA and PSA were performed to characterize and quantify the potential effects of parameter uncertainties and assumptions on ICER estimation.

4.4.1 One-way deterministic sensitivity analysis

The parameter values and uncertainties have been summarized in Table 15 previously. The tornado diagram integrated the model outputs from multiple one-way DSA. Parameters were presented nominally according to their impact on the ICER values. As shown in Figure 9, parameters were varied within their range, one at a time while holding other parameters constant, and each bar indicates one parameter's uncertainty and its impact on the range of ICER values.

1-way DSA, determined that the ICER was most sensitive to four factors:

1. Average number of metastases requiring SABR treatment before progression (ICER: $28,066 to $64,429/QALY);

2. Relative risk of chemotherapy utilization in patients receiving the SABR+ SoC as compared to patients receiving SoC alone (ICER: $27,173 to $53,738/QALY);

3. Hazard ratio of PFS among patients in SABR+ SoC arm as compared to the SoC arm during the lifetime (ICER: $31,548 to $53,273/QALY);

4. Hazard ratio of OS among patients in SABR+SOC arm as compared to the SoC arm after having progressed (ICER: $32,802 to $50,014/QALY).

The increased number of metastases treated within SABR can result in higher expenditure on SABR strategies. The relatively growing needs of chemotherapy in SABR arm also increased the costs within the SABR arm. There were more accumulated costs over the lifetime of SABR-treated patients, resulting from improved survival, as compared to the patients received SoC alone. Therefore, parameter uncertainties including the number of metastases and chemotherapy utilization influenced the cost differences between 2 strategies and consequently affected the ICER value.

On the other hand, the hazard ratio of PFS, which can be interpreted as the immediate risk (rate) of developing cancer progression at any time point among patients in SABR+

SoC arm as compared to the SoC arm over lifetime, influenced the ICER via a complex effect on progression and survival patterns, as well as costs and utilities. The overall effect of HR of PFS is positively correlated to the ICER value. In other words, with a higher HR there was a decreasing survival benefit among SABR-treated patients. Consequently, SABR was less likely to be cost-effective, since the health benefit gained by SABR was less likely to be justified by the incurred cost. The hazard ratio of post-progression survival is also positively related to the ICER value. As the HR increased, the survival benefit of patients receiving SABR+SoC strategy decreased, suggesting SABR was less likely to be cost-effective.

In all DSA performed, all predicted ICERs, even in extreme scenarios, yielded a value below the a priori, WTP threshold of $100,000/QALY (Figure 9).

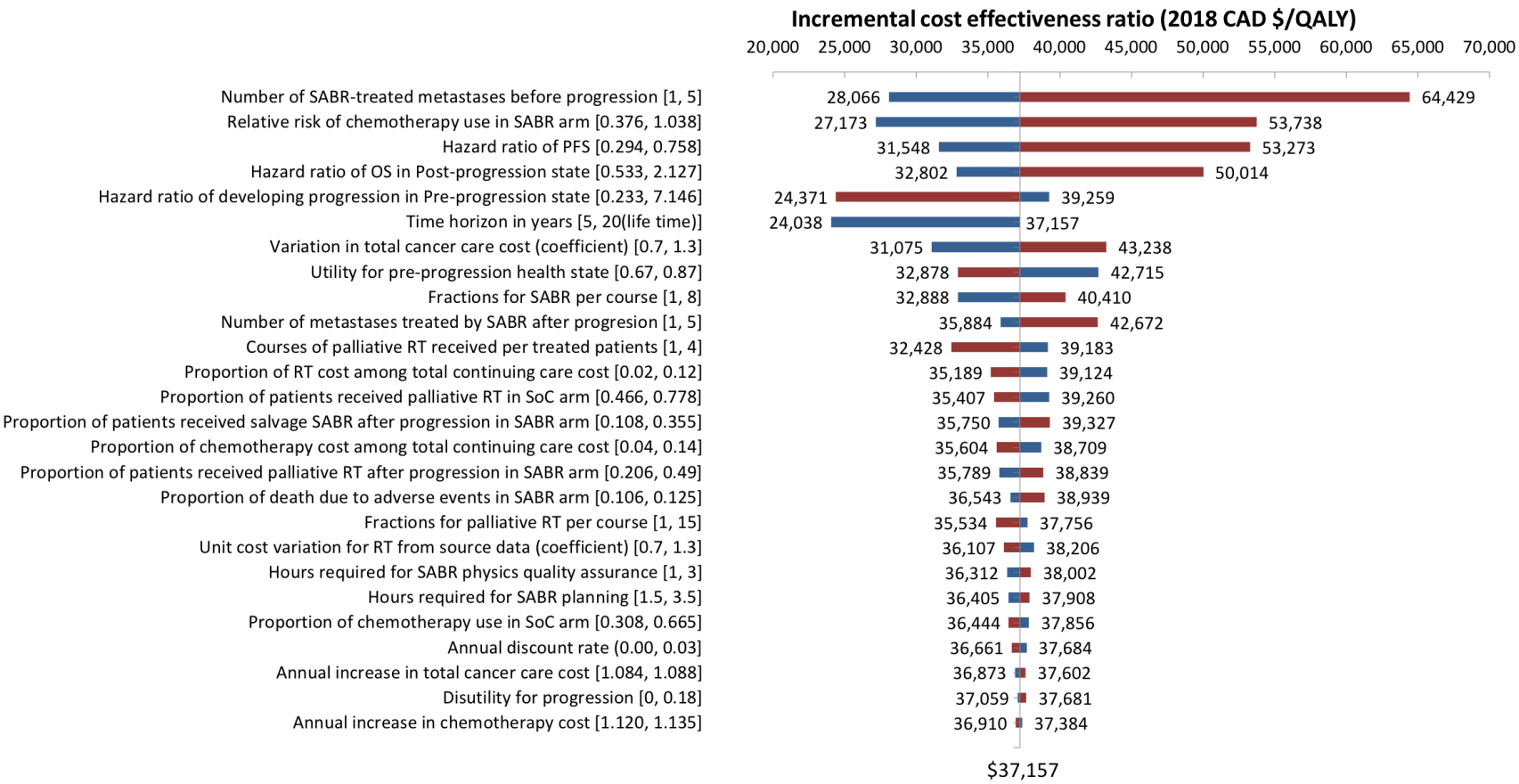


Figure 9. Incremental cost-effectiveness ratio Tornado diagram

Abbreviations: No., number of; SoC, standard of care; SABR, stereotactic ablative body radiotherapy; palRT, palliative radiotherapy; PFS, progression- free survival; RT, radiation therapy;
Bars in red indicate the direction of parameter value increase, while bars in blue indicate the parameters decreasing within the range of the uncertainties.

4.4.2 Two-way deterministic sensitivity analysis

We performed specific two-way DSA based on clinical experience on the two factors that would have the largest impact on the model: 1) the increasing cost for SABR treatment as a result of an increasing number of metastatic sites and 2) the clinical efficacy associated with SABR treatment. Although SABR-COMET evaluated up to 5 metastases, we extended the testing range to 10 metastases for hypothesis generation. As progression-free survival may be associated with the number of metastases, we varied the number of metastases before progression and the HR of PFS simultaneously, and within their uncertainty range to explore their impact on the ICER at WTP thresholds of $100,000/QALY. The results are illustrated in Figure 10.

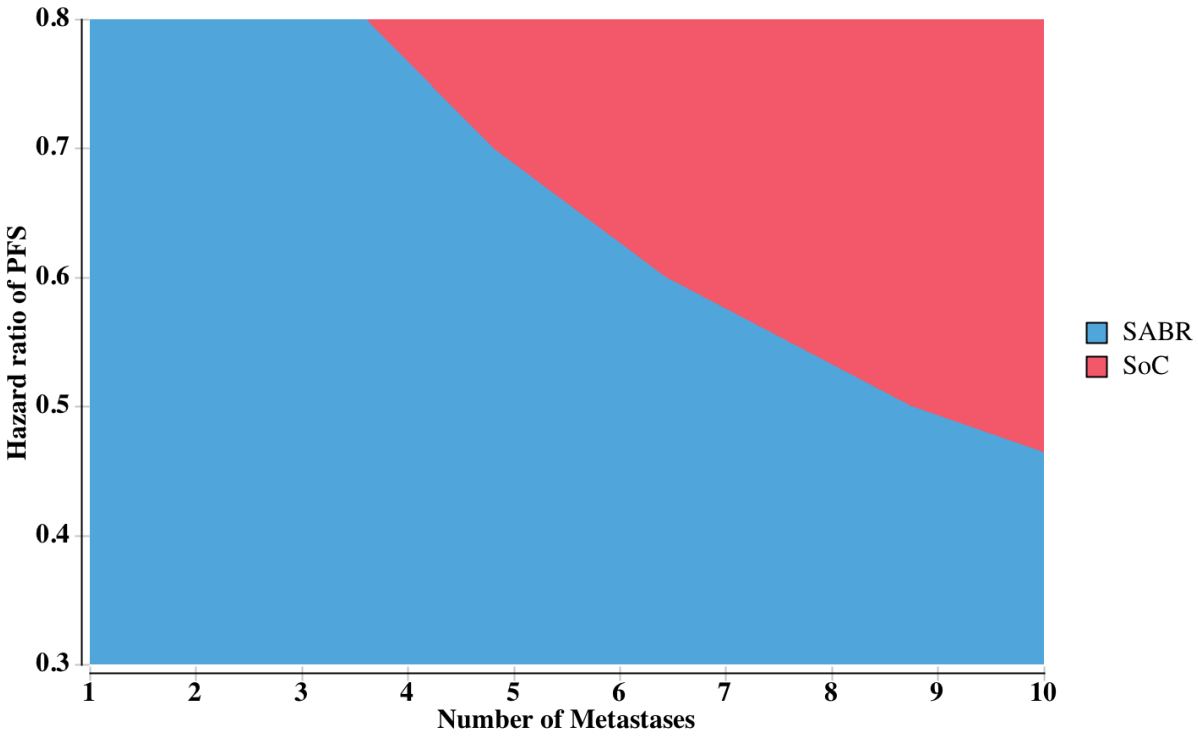


Figure 10. Two-way sensitivity analysis

The border between the red and blue areas represents the sensitivity threshold in which the ICER is equivalent to the WTP. The blue area represents various pairs of values where SABR is considered cost-effective, whereas the red area illustrates joint distributions of 2 parameter that suggesting the SoC strategy be cost-effective.

The two-way sensitivity analysis of number of metastases and HR of PFS revealed that SABR is the preferred strategy at a threshold of three metastases across the 95% CI of the PFS HR reported in the SABR-COMET trial (0.29-0.76). In patients with four metastases, a PFS HR of at least 0.72 is required in order for SABR to be cost-effective. Beyond four metastases, a non-linear relationship between increasing number of lesions and PFS HR was observed, whereby a 0.05 decrease in HR is required for every additional metastasis. Finally, the PFS HR would need to be below 0.46 for 10 metastases in order for the SABR strategy to be cost-effective at a WTP threshold of $100,000/QALY.

4.4.3 Probabilistic sensitivity analysis

The PSA was performed to vary all model inputs simultaneously to evaluate the robustness of the parameter and distribution uncertainties on the results. A total of 5000 Monte Carlo simulations were performed, sampling randomly from all distributions of the model inputs in each iteration. The ICER scatter plot in Figure 11 was generate based on 5000 iterations. In the majority (97%) of iterations, the ICER values was lower than the WTP threshold, distributed within the quadrant I. Therefore SABR+ SoC is associated with a health benefit at a higher cost as compared to the SoC alone, and SABR is cost-effective most of the time at a WTP threshold of $100,000/QALY.

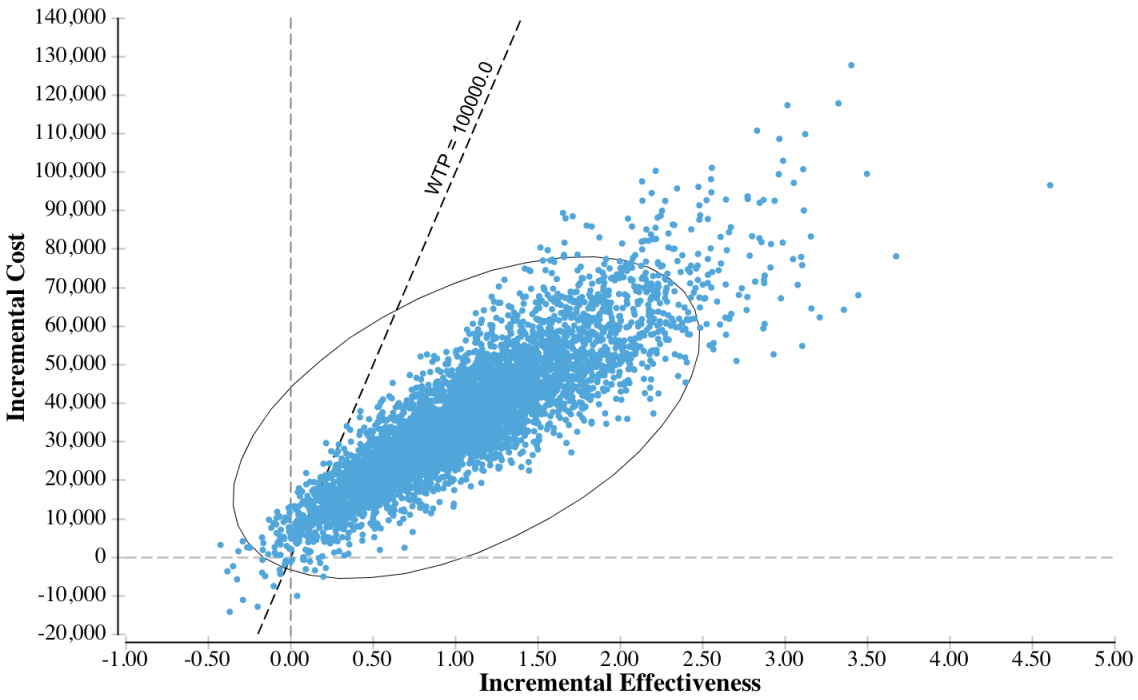


Figure 11. Probabilistic scatter plot of ICER, SABR+ SoC vs. SoC

A cost-effectiveness acceptability curve, which describes the likelihood of a strategy being cost-effective at different WTP thresholds is depicted in Figure 12. When the $50,000/QALY threshold is adopted, the SABR+ SoC strategy is considered as cost-effective in 87% of the iterations, while at a threshold of $100,000/QALY, it is cost-effective 97% of the time.

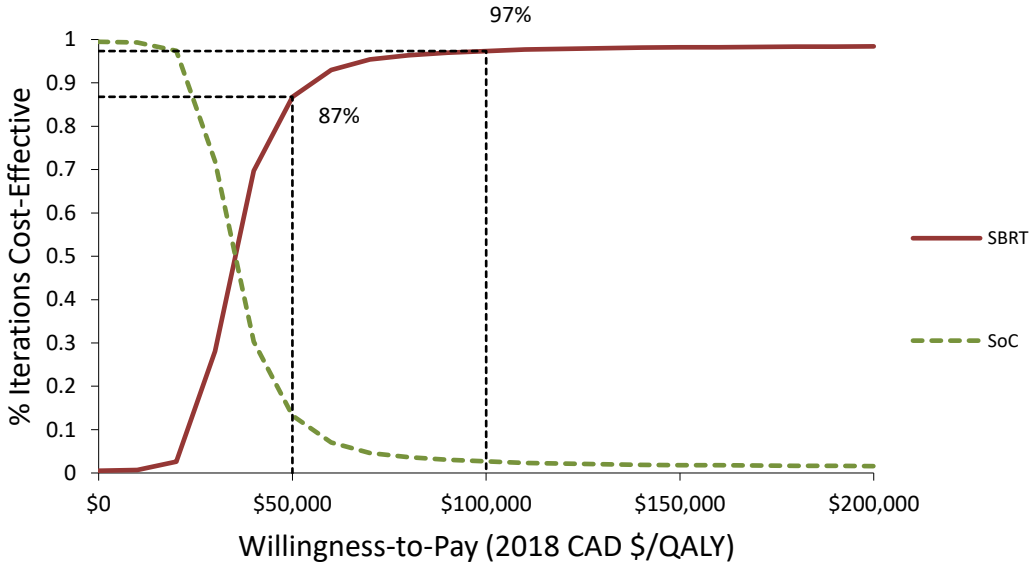


Figure 12. Cost-effectiveness acceptability curve

Chapter 5

5 Discussion and conclusion

5.1 Summary of findings

This analysis of oligometastatic cancer patients was created from individual-patient data from the SABR-COMET trial, supplemented by data from the available medical literature. It was both internally and externally validated and suggested that SABR+SoC is cost-effective from the Canadian healthcare payer perspective, with a base-case ICER of $37,157/ QALY. This result can be interpreted that SABR costs less than average required in health care system to exchange for 1 unit of QALY, and therefore the incremental cost can be justified by the health benefit gained. In sum, the combination of SABR with current standard of care was considered as cost-effective from the Canadian health care system perspective under the base-case scenario in which all conditions, except for the lifetime horizon, approaches to the clinical trial.

A wide-range of DSA were performed, and the ICER was most impacted by 4 factors: the number of SABR-treated metastases before progression (ICER $28,066-64,429/QALY); the relative risk of chemotherapy utilization in patients receiving the SABR+ SoC (ICER $27,173-53,738/QALY); the hazard ratio of PFS among patients in SABR+ SoC strategy as compared to the SoC strategy (ICER $31,548-53,273/QALY); and the hazard ratio of OS in post-progression state (SoC strategy as the reference group) (ICER $32,802-50,014/QALY). Nonetheless, even in these extreme ranges, the ICER remained below a WTP of $100,000 QALY gained. Furthermore, PSA was performed, and the finding that SABR + SoC was cost-effective remained true for most iterations at the $100,000/QALY WTP threshold, suggesting robustness of the model.

5.2 Internal validity and generalizability

A modeling-based CEA was used in our study. The transition probabilities were derived from individual-level patient data from the RCT that provides high quality evidence. However, the utilities, disutilities and costs were not collected in the SABR-COMET trial and their values and potential ranges were derived from published literature.

One of the main strengths of modeling-based CEA in the decision analysis was that it allowed us to extrapolate the 5-year follow-up duration of the trial into a life time horizon which is recommend in CEA by a recent guideline [58]. Otherwise, the time horizon bias may be introduced when the future ICER no longer equal to the ICER over the 5-year duration [81]. Our analysis (Figure 8) demonstrated that using a 5-year horizon resulted in a lower ICER value and biased the result towards a direction, suggesting the SABR strategy would be more cost-effective within 5 years as compared to a lifetime horizon. Because the longer patients survive, the higher costs, associated with inpatient hospitalization, same-day surgery, physician services, home and community care, diagnostic tests, out-patient prescription drugs and chemotherapies, may incur.

Another strength of modeling-based CEA in our study was that the costs data from populations-based studies represent a payer's perspective, and therefore we avoided the bias introduced by protocol-driven costs which are trial related and can hardly occur in the routinely clinical practice [82].

Nevertheless, there were several concerns related to the model-based method including parameter uncertainties, structural uncertainties and methodological uncertainties. Firstly, there were lacking perfect knowledge about the true value of model parameters, known as parameter uncertainty, as the utilities, disutilities and costs were derived from different publications. Parameter uncertainties were addressed by deterministic and probabilistic sensitivity analysis in our study. Furthermore, the model structural and methodological uncertainties were also exist [83].

Secondly, modeling and structural uncertainties are related to the framework of the model such as the included health states, functional form of transition probabilities and other model inputs [83]. We considered this type of uncertainty is of less concern since we validated our model internally and externally. The simulated survival and progression pattern fitted well with those patterns from the SABR-COMET trial as well as other studies with similar populations (result 4.3.1). We fitted the model with a Weibull distribution since it has a simple functional form and was widely used, and it provides hazard ratio that can be compared with the hazard ratio from the clinical trial. Goodness-

of-fit, which evaluated how similar the modeled survival curves were with the real survival curves from the trial, were examined in a qualitative way through visual comparison.

Thirdly, methodological uncertainties in our study mainly related to the process of deriving unit costs and mapping utility. These methodological uncertainties were addressed via sensitivity analysis by define parameter ranges which consider to be enough to cover the potential variation of the parameters. According to the result of sensitivity analysis, the methodological uncertainties didn't change our result qualitatively.

Generalizability refers to the consistency whereby the cost-effectiveness of SABR strategy in other countries, provinces and /or healthcare systems can be inferred from our findings. The aim of this study was to inform the health care decision from Canadian health care system perspective. We used population-based cost of Ontario to indicate the cancer care cost of Canada. In addition, although the SABR-COMET trial was an international multi-center trial, the Canadian participants accounted for about 80% of the trial cohort, with around 65% of Canadian patients were recruited from one cancer center in Ontario [43].

Cancer care expenditures by government payers may vary across Canada and the world due to the diversity of coverage policies, payment of physicians and unit cost on the treatment etc. Our estimation of unit cost of SABR via activity-based method ($8,378 in 2018 CAD), was consistent with the SABR cost of Ontario from previous studies [46, 47], but lower than the SABR cost in most of other jurisdictions (including the US), where costs ranged from $6,521 to $19,603 (2014 US dollars), according to a systematic review that summarized the different type of RT cost per treatment [84]. The palliative RT cost $5,736 (2018 CAD) per patient, which was similar to other Canadian estimates [46, 47], but lower than the reported 3D-CRT costs in US varied from $5,583 to $90,055 (2014 US dollars), suggesting a highly diversified cost for palliative RT per treatment. However, even if the unit cost of SABR increased to $90,055 (2014 US dollars), equivalent to $23,830 (2018 CAD), the ICER value would be $40,152/ QALY gained.

This is still lower than the willingness-to-pay threshold of $100,000/QALY gained, suggesting that administrating SABR would be a cost-effective strategy.

The relative proportion of patients who received the systemic therapy between the two strategies also influenced the generalizability of our findings. SABR as an effective local treatment may decrease the receipt of systemic therapy and the number of cycles of further systemic therapy were initially considered as secondary outcome in the SABR-COMET trial. However, this endpoint was not ascertained as patients received treatment at other centers, and the receipt of systemic therapy were tested as a binary outcome, whereby the proportion of receipt of systemic therapy were not statistically differ between strategies. In addition, SABR-COMET trial was conducted in an era where more effective therapies, such as targeted therapy and immunotherapy, as compared to chemotherapy were not routinely utilized. Therefore, in our study, we only modelled the proportion of receipt of chemotherapy. According to our DAS, the higher the proportion of SABR-treated patients averted from receiving chemotherapy, the lower cost was associated with SABR strategy and the more likely SABR remain cost-effective. This may be the same with other types of systemic therapy and should be explored in future research.

5.3 Limitations

Costs data in this study were identified from the publications. Therefore, direct medical cost was the only type of healthcare cost that has been included in this cost-effectives analysis. Indirect cost was not incorporated due to the lack of available data. The reported outpatient drug costs excluded the spending among individuals age below 65. The cost of emergency department visits or other ambulatory care were also excluded. Therefore, the base cost in our study may be underestimated from the Canadian health care system perspective. However, the higher the base cost the smaller the estimated ICER value would be, according to the result of deterministic sensitivity analysis. Therefore, this issue did not change our finding qualitatively at a WTP threshold of $100,000/QALY gained.

Bias may have been introduced in the utility mapping process since the source population where mapping algorithm were developed may not fully represent our study population (lack of exchangeability). Efforts were made to select mapping model from study of which the population most likely to representing the cohort in our research. Furthermore, we examined the uncertainty of utility inputs via deterministic and probabilistic sensitivity analysis. The result demonstrated that the utility uncertain is unlikely to result in qualitative change to our conclusion.

The heterogeneity is an inherited limitation in this study. The SABR-COMET trial included cancer patients with mixed type of primary tumor, and the sample size was small in subgroups defined by primary cancer. In this situation, subgroup analyses were with limited ability to produce reliable and unbiased model predictions. We assumed that the ICER is constant across all of the subpopulations, and therefore used one functional form to modeling the whole cohort. However, we value the importance of tailoring the cost-effectiveness information to a specific decisions-making setting with limited heterogeneity and highly recommend that subgroup analysis to be done in the future studies.

The SABR-COMET trial adopted phase 2 screening design with a pre-specified two-sided significance level of 0.20. The median overall survival for SABR-treated patients were 1.5 times of the SoC recipients with a p=0.090, meeting the pre-specified end point to proceed with the phase III trial. Nevertheless, this p-value does not meet the typical definition for statistically significance of a two-sided α of 0.05. Therefore, a cost-effectiveness analysis based on evidences with higher quality such as the on-going phase III randomized controlled trial with larger sample size (NCT03721341), would be highly recommend once the data is mature.

Finally, the PSA were performed based on a strong assumption of independent distributions for all model petameters [72]. Given that our costs and utilities were derived from literature, it was impossible to model dependent probabilities in PSA. Therefore, the potential correlation between parameters would be unclear.

5.4 Conclusion

This model-based cost-effectiveness analysis evaluated SABR+ SoC compared to SoC alone for oligometastatic cancer patients based on individual-level patient data from phase II randomized controlled trial, published costing and utility analysis and published mapping studies. Our findings suggest that SABR is highly cost-effective at the willingness-to-pay threshold of $100,000/QALY from the Canadian health care system perspective for cancer patients with 1-5 oligometastatic lesions compared to the standard of care.

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Appendices

Appendix A: Glossary of terms and definitions of Markov rewards in the model (Summarized in Table 3)

Base care cost: one of the three components of the total direct medical cost which otherwise include radiotherapy cost and chemotherapy cost.

Base terminal care cost: the base care cost of terminal care phase.

Base continuing care cost: the base care cost of continuing care phase.

Continuing care: a phase of health care, which happened between the initial 6 months after diagnosis and the last 12 months before death, mainly include surveillance and active follow-up treatment for both new primary cancer and recurrent cancer.

Terminal care: a phase of health care, which refers to the last 12 months before death, often characterized by intensive palliative services.

ΔTerminal care cost: the cost difference between terminal care and cornuting care. In our model the variables were assigned to each death-related health states as a one-time event cost to capture the incremental cost of patient care within the last year of life. Adding the incremental cost to the quarterly accumulated continuing cost obtains the total cost within the last 12 months before death of the cohort.

Palliative RT cost: the average cost of palliative radiotherapy for SABR and SoC strategies in pre-progression and post-progression health states.

SABR cost: the average cost of SABR for SABR strategy in pre-progression and post-progression health states.

AE cost: the average cost of managing treatment-related adverse events, for SABR and SoC strategies. All available records of treatment-related adverse events, including fatigue, pain and dyspnea occurred within pre-progression health state.

Disutility: the decrement of health state utility due to the occurrence of treatment-related adverse events.

Pre-progression utility: the mean utility related to each strategy in the pre-progression health state.

Post-progression utility: the mean utility related to each strategy in the post-progression health state.

Appendix B: National cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC-AE) Scoring version 4.0

Available at:

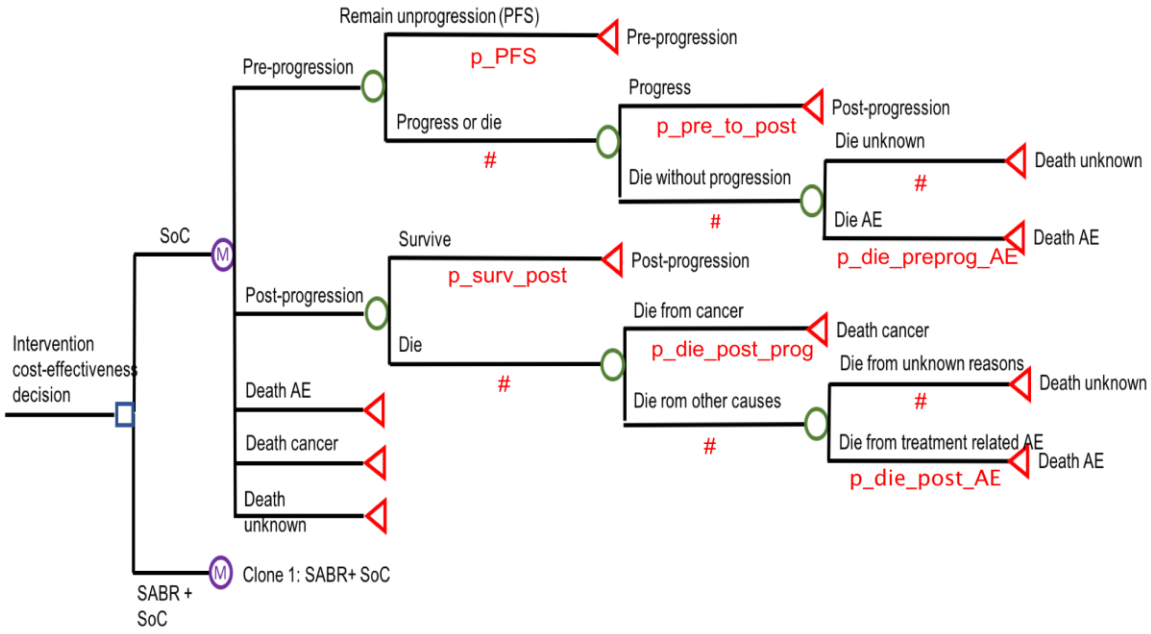
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Appendix C: Consolidated Health Economic Evaluation Reporting Standards - CHEERS Checklist

Available at:

https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/article/consolidated-health-economic-evaluation-reporting-standards-(cheers)---explanation-and-elaboration

Appendix D: Construction of transition probabilities



SoC strategy:

p_PFS_1:

1- (exp (- (_stage * exp (-n_beta_PFS$^{\#}$ * arm_1-n_intercept_PFS$^{\#}$)) ^ n_shape_PFS$^{\#}$) - exp (- (t * exp (-n_beta_PFS$^{\#}$ * arm_1 - n_intercept_PFS$^{\#}$)) ^ n_shape_PFS$^{\#}$)) / exp (- (_stage * exp(-n_beta_PFS$^{\#}$ * arm_1 - n_intercept_PFS$^{\#}$)) ^ n_shape_PFS$^{\#}$)

p_pre_to_post_1:

1 - (exp (- (_stage * exp(- n_beta_Pre_to_Post$^{\#}$ * arm_1 -n_intercept_Pre_to_Post$^{\#}$)) ^ n_shape_Pre_to_Post$^{\#}$) – exp (- (t * exp (-n_beta_Pre_to_Post$^{\#}$ * arm_1 - n_intercept_Pre_to_Post$^{\#}$)) ^ n_shape_Pre_to_Post$^{\#}$)) / exp (- (_stage*exp (- n_beta_Pre_to_Post$^{\#}$ * arm_1 - n_intercept_Pre_to_Post$^{\#}$)) ^ n_shape_Pre_to_Post$^{\#}$)

p_die_preprog_AE_1:

by definition, patient in control arm should not die of SABR AE. But may die of palRT. Value equals 0.0025

p_surv_post_1:

1 - (exp (- (t_post * exp (- n_beta_surv_post$^{\#}$ * arm_1 - n_intercept_surv_post$^{\#}$)) ^ n_shape_surv_post$^{\#}$) – exp (- (_tunnel*exp (-n_beta_surv_post$^{\#}$ * arm_1 - n_intercept_surv_post$^{\#}$)) ^ n_shape_surv_post$^{\#}$)) / exp (- (t_post * exp (- n_beta_surv_post$^{\#}$ * arm_1 - n_intercept_surv_post$^{\#}$)) ^ n_shape_surv_post$^{\#}$)

p_diepostprog_1:

1 - (exp (- (t_post * exp (- n_beta_diepostprog$^{\#}$ * arm_1 - n_intercept_diepostprog$^{\#}$)) ^ n_shape_diepostprog$^{\#}$) – exp (- (_tunnel*exp (-n_beta_diepostprog$^{\#}$ * arm_1 -

n_intercept_diepostprog[#])) ^ n_shape_diepostprog[#])) / exp (- (t_post * exp (- n_beta_diepostprog[#] * arm_1 - n_intercept_diepostprog[#])) ^ n_shape_diepostprog[#])

p_diepost_AE_1: assuming for post-progression patients who didn't die from cancer, 2.5% of them will die from AE in SoC arm (rare case assumption). Value equals 0.025.

SABR + SoC strategy:
p_PFS:
1 - (1 - exp (n_HR_PFS[#] * ln (1 - (1 - p_PFS_1)))) - p_SA_death_AE_2

p_pre_to_post:
if (1 - (1 – exp (n_HR_Pre_to_Post[#] * ln (1 - (1 - p_Pre_to_Post_1)))) > 1; 1; 1 - (1 – exp (n_HR_Pre_to_Post[#] * ln (1 - (1 - p_Pre_to_Post_1)))))

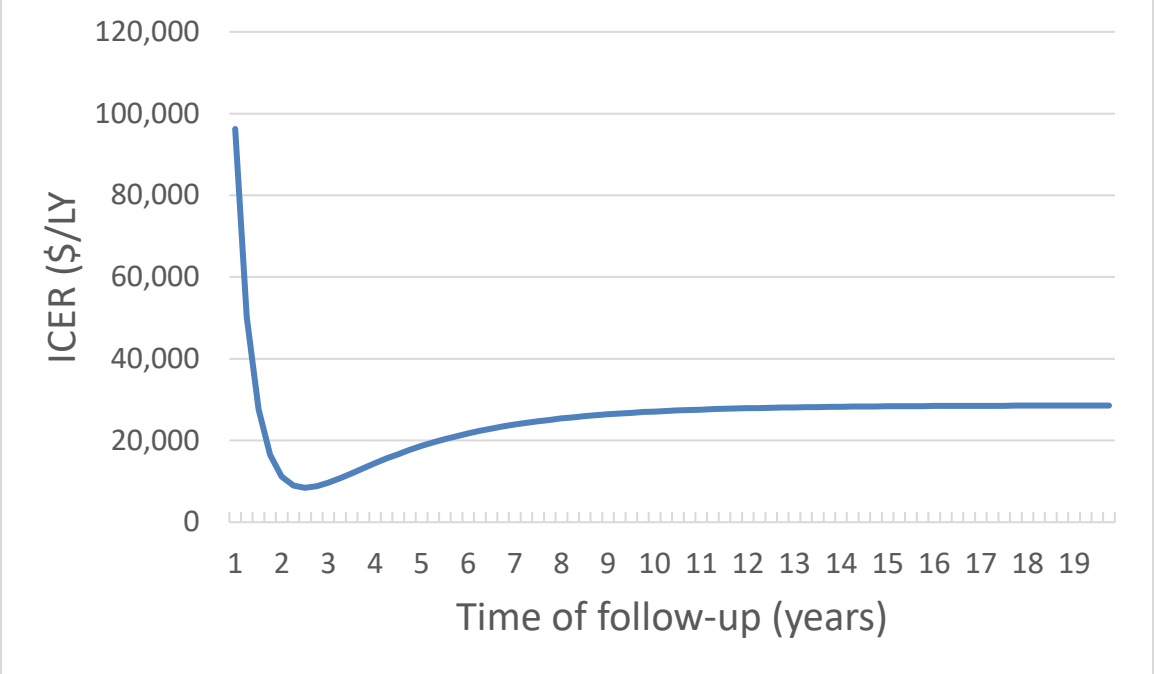
p_die_preprog_AE:
(s_p_preprog_dieAE_2) * 66 / (s_p_preprog_dieAE_2 * 66 + 1)
where s_p_preprog_dieAE_2= 0.045 (Proportion of death 3/66 due to adverse effect in SABR arm);
p_surv_post:
1 - (1 – exp (n_HR_surv_post[#] * ln (1 - (1 - p_surv_post_1))))

p_diepostprog:
1 - (1 – exp (n_HR_diepostprog[#] * ln (1 - (1 - p_diepostprog_1))))

p_diepost_AE:
assuming for post progression patients who didn't die from cancer, 2.5% of them will die from AE in SABR+SoC arm (rare case assumption). Value equals 0.025.

Notes: "_stage" equals number of model cycles; "_tunnel" accounts for time in relevant states; "t_post" equals to "_tunnel-1"; arm_1 = 0.
Transition probabilities which derived via parametric survival analysis with Weibull distribution, were time dependent. Rare cases were directly assigned with small probabilities of 2.5%, since, in such case, survival analyses were with limited ability to produce valid model prediction.
indicate parameters obtained via parametric survival analysis with Weibull distribution based on individual-level patient data from SABR-COMET trial

Appendix E: ICER($/LY) of SABR+SoC versus SoC alone over time)



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1. Chen L, Chen Y, Li B. The efficacy and safety of proton-pump inhibitors in treating patients with non-erosive reflux disease: a network meta-analysis. Sci Rep. 2016 Sep 1; 6:32126.
2. Chen YJ, Chen LX, Han MX, Zhang TS, Zhou ZR, Zhong DS. The efficacy and safety of chemotherapy in patients with non-small cell lung cancer and interstitial lung disease: a PRISMA-Compliant Bayesian meta-analysis and systematic review. Medicine. 2015 Sep; 94(36): e1451.