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Original Article

# Cost-effectiveness Analysis of Stereotactic Radiosurgery Alone Versus Stereotactic Radiosurgery with Upfront Whole Brain Radiation Therapy for Brain Metastases

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## Abstract

*Aims:* Stereotactic radiosurgery (SRS) alone or upfront whole brain radiation therapy (WBRT) plus SRS are the most commonly used treatment options for one to three brain oligometastases. The most recent randomised clinical trial result comparing SRS alone with upfront WBRT plus SRS (NCCTG N0574) has favoured SRS alone for neurocognitive function, whereas treatment options remain controversial in terms of cognitive decline and local control. The aim of this study was to conduct a cost-effectiveness analysis of these two competing treatments.

*Materials and methods:* A Markov model was constructed for patients treated with SRS alone or SRS plus upfront WBRT based on largely randomised clinical trials. Costs were based on 2016 Medicare reimbursement. Strategies were compared using the incremental cost-effectiveness ratio (ICER) and effectiveness was measured in quality-adjusted life years (QALYs). One-way and probabilistic sensitivity analyses were carried out. Strategies were evaluated from the healthcare payer's perspective with a willingness-to-pay threshold of $100 000 per QALY gained.

*Results:* In the base case analysis, the median survival was 9 months for both arms. SRS alone resulted in an ICER of $9917 per QALY gained. In one-way sensitivity analyses, results were most sensitive to variation in cognitive decline rates for both groups and median survival rates, but the SRS alone remained cost-effective for most parameter ranges.

*Conclusions:* Based on the current available evidence, SRS alone was found to be cost-effective for patients with one to three brain metastases compared with upfront WBRT plus SRS.



*Key words:* Brain metastases; cost-effectiveness; SRS; WBRT; willingness-to-pay

## Introduction

Brain metastases occur in up to 40% of patients with cancer. Most patients present with oligometastatic intracranial disease with one to three brain lesions [1]. For such patients, surgery, whole brain radiation therapy (WBRT) and/or stereotactic radiosurgery (SRS) have been mainstays of palliative treatment [2]. Although radiation therapy has been shown to reduce the morbidity from intracranial tumours, it also adversely affects neurocognitive function with an associated impact on quality of life (QOL) [2–4].

SRS enables the precise delivery of high-dose radiation in a single fraction treatment. This modality has become increasingly utilised for the management of brain metastases. However, as SRS is so highly focused at the visible metastases, failure in other parts of the brain may be frequent. To address this, SRS combined with WBRT (typically with 10 or 14 fractions) has been used. This achieves an improved intracranial tumour control compared with SRS alone, but at the cost of greater neurocognitive deterioration than SRS alone [5–7]. Therefore, the optimal management of brain metastases patients has remained controversial due to uncertain trade-offs between potential benefits of improved local control from upfront WBRT versus its negative impact on neurocognitive function [8–11].

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Clinicians are increasingly assessing QOL to evaluate the overall efficacy and applicability of any treatment modality. Particularly in cancer trials with new treatment technologies, QOL becomes one of the most important measures for treatment outcome [12,13]. Several randomised clinical trials for brain metastases patients comparing SRS plus upfront WBRT with SRS alone have shown no survival difference between two treatment modalities [14–17]. In this context, QOL is a very important concern for the choice of treatment options because treatments are mainly for palliation of symptoms [13,18,19].

Given the higher cost, additional treatment time, improved intracranial tumour control, worse neurocognitive function and no survival advantage for upfront WBRT plus SRS compared with SRS alone, it is unclear which treatment option is a better choice in terms of not only favourable clinical outcome but also from a cost-effectiveness perspective. Global interest in economic evaluation for treatment options has also been increasing significantly due to changes in the health care environment [20]. A cost-effectiveness analysis (CEA) is a mathematical representation of clinical events that occur over time, comparing total costs and QOL between two or more treatment strategies. Thus, it is an important tool for incorporating economic considerations into clinical decisions [21]. Recently, The American Society for Radiation Oncology (ASTRO) Choosing Wisely® campaign, supported by analyses of randomised prospective trials, has recommended SRS alone over upfront WBRT with SRS for limited brain metastases [22]. Recent multi-institutional randomised clinical trial results comparing SRS alone with upfront WBRT plus SRS (NCCTG N0574) [17] reported both clinical effectiveness and QOL, including neurocognitive deterioration measures, as did a previous large randomised trial in Europe (EORTC 22952-26001) [16]. Both trials reported similar results: (i) no survival difference between the two treatment strategies, (ii) more cognitive deterioration with upfront WBRT and (iii) better intracranial local control for upfront WBRT, resulting in less salvage treatment. In addition, quality of life utility values, including neurocognitive decline directly measured in brain metastases patients for SRS and WBRT have recently been published, which were previously unavailable [23]. Therefore, here we carried out a CEA comparing SRS alone with SRS plus WBRT for brain metastases patients with one to three lesions using all available evidence base patient level data.

## Materials and Methods

### *Decision Model*

We used published clinical data largely from randomised clinical trials and utility values for this study. We constructed a Markov state transition model using TreeAge Pro Suite 2016 software (TreeAge Software, Williamstown, MA, USA) to carry out a CEA. In the model, identical hypothetical brain metastases patient cohorts with one to three brain lesions from oligometastatic disease were treated with single fraction SRS or single fraction SRS plus 10 fractions of WBRT. The mean age of the cohorts was 60 years old [14–17]. Cohorts were followed for 60 months and the Markov cycle length was 1 month. The Markov model is shown in Figure 1, with transitions between health states represented by arrows. Transition probabilities between health states and clinical parameters were based on four randomised clinical trials and a literature review (Table 1) [14–17]. To ensure the validity of the Markov model, calibration was carried out by calculating the overall survival and intracranial progression rates, resulting in values comparable with published results (Table 1).

Initial treatment occurred in the first cycle of the model (Figure 1). Patients who were alive after the initial treatment could transition to three states: intracranial tumour progression, other progression or no disease progression. In subsequent cycles, a subset of the cohort in the no disease progression state could remain in that state or transition to tumour progression (intracranial or other). Those with intracranial progression received salvage treatment based on the retreatment rates from published data (Table 1). Those not having salvage treatment and those with recurrence after salvage treatment transitioned to the other progression state. Similarly, those without recurrence after salvage treatment could stay in that state over time or transition to the other progression state. Retreatment occurred only once after intracranial progression. Mortality for both groups was assumed to be equal, based on survival rates from randomised clinical trials [14–17]. Future costs and utilities were discounted at an annual rate of 3%. The base case model was constructed from a payer's perspective for health care services [24], using 2016 Medicare reimbursement rates [25].

### *Model Assumptions*

The median survival was set equal for both treatment groups as 9 months. Salvage treatment occurred only once after intracranial progression assuming that either SRS or WBRT were used for the SRS alone strategy and only SRS for the WBRT plus SRS strategy. Magnetic resonance imaging

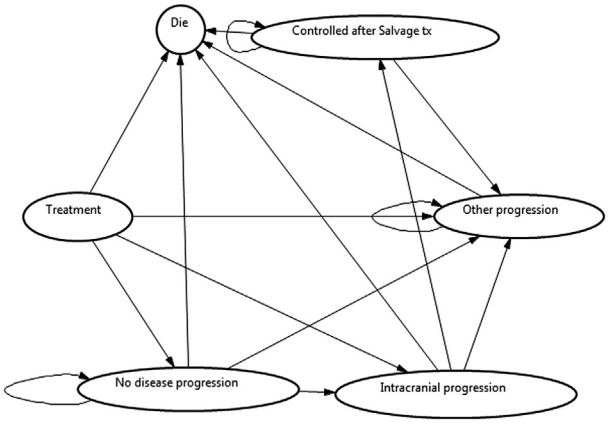


**Fig 1.** Bubble diagram for the Markov state transition model.

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