Comparative Effectiveness Analysis of Treatment Options for Single Brain Metastasis

Kristopher T. Kimmell[1], Emily LaSota[2], Robert J. Weil[3], Nicholas F. Marko[3]

BACKGROUND: **Brain metastases (BMs) occur in up to 30% of patients with cancer. Treatments include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS), alone or in combination. Although guidelines exist, data to inform individualized approaches to therapy remain sparse. We sought to compare semiquantitatively the effectiveness of various modalities in the treatment of single brain metastasis.**

METHODS: **We performed a comparative effectiveness analysis (CEA) that integrated efficacy, cost, and quality of life (QoL) data for alternate BM treatments. Efficacy data were obtained from a comprehensive review of current literature. Cost estimates were based on publicly available data. QoL data included the Karnofsky Performance Status (KPS) and other questionnaires. Six treatment strategies using combinations of surgery, WBRT, and SRS were compared with decision tree software.**

RESULTS: **The clinical efficacy, cost, and QoL effects of each strategy were scored semiquantitatively. We constructed a model to integrate individual preferences regarding the relative importance of efficacy, QoL, and cost to provide personalized rankings of the effectiveness of each strategy.**

CONCLUSION: **The choice of strategy must be individualized for patients with a single BM. Our CEA and decision model combines empirical data with patient priorities to produce a ranking of alternate management strategies.**

INTRODUCTION

Brain metastases (BMs) are a common complication of cancer. More than 100,000 new cases of BM are diagnosed annually (10). The incidence is difficult to calculate but appears to be increasing due to multiple factors (10). BMs are a primary cause of morbidity and mortality in cancer (10) and an indicator of progressive disease (24).

Prognosis for patients with BM has been estimated by the Recursive Partitioning Analysis (RPA) method (11), the Graded Prognostic Assessment (GPA) (49), and the Diagnosis-Specific GPA (50). These scales suggest that favorable prognostic factors include younger age, higher Karnofsky Performance Status (KPS), fewer brain lesions, and absence or control of extracranial disease.

Nearly half of patients have a single brain lesion at diagnosis (10). Single BM may be amenable to several therapies including surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS), while patients with multiple BM are traditionally treated with WBRT or SRS. Although treatment guidelines exist for BM (10, 15), there remains no uniform standard of care. Numerous studies have assessed the efficacy of monotherapy or combinations of two

Key words

- Comparative effectiveness research
- Cost
- Efficacy
- Karnofsky Performance Status
- Metastatic tumors
- Quality of life
- Single brain metastases
- Single metastasis

Abbreviation and Acronyms

AHRQ: Agency for Healthcare Research and Quality
BM: Brain metastasis
CEA: Comparative effectiveness analysis
GPA: Graded Prognostic Assessment
HCUP: Healthcare Cost and Utilization Project
ICD-9-CM: International Classification of Diseases, 9th edition, Clinical Modification
ICER: Incremental cost-effectiveness ratio
KPS: Karnofsky Performance Status
QALY: Quality-adjusted life-year
QoL: Quality of life
RPA: Recursive partitioning analysis
SE: Standard error
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiotherapy

From the [1]Department of Neurosurgery, University of Rochester Medical Center, Rochester, New York, USA; [2]Indiana University School of Medicine, Indianapolis, Indiana, USA; and [3]Department of Neurosurgery, Geisinger Health System, Danville, Pennsylvania, USA

To whom correspondence should be addressed: Kristopher T. Kimmell, M.D.; Requests for reprints and other Correspondence: Robert J. Weil, M. D., Chief Medical Executive, Geisinger Northeast, 1800 Mulberry Street, 4th Floor POB, Scranton, PA, USA 18510
[E-mail: kristopher_kimmell@urmc.rochester.edu]

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therapies (Table 1), but evidence-based comparisons of alternative treatment strategies for BM are lacking (51). Efficacy is not the only domain relevant to the management of patients with BM (24, 25). Oncologists regularly integrate efficacy, QoL, and cost when crafting a treatment plan for patients.

We perform a two-step comparative effectiveness analysis (CEA) of treatment options for BM. First, we create a decision tree that offers potential therapeutic strategies for patients with BM. Second, we conduct an evidence-based CEA of current literature regarding efficacy, QoL, and cost of therapies.

METHODS

We analyzed therapeutic strategies for patients with single BM such that SRS, surgery, WBRT, or combination therapy would be reasonable options. A focal lesion allows several modalities to be considered.

Three domains were chosen to evaluate treatment strategies: clinical efficacy, cost, and QoL. Side effects and morbidity associated with treatments were also considered. We considered both equal and unequal weighting strategies for these domains, and clinician and patient preference for a given domain is addressed in the discussion. A decision tree was constructed on the basis of treatment guidelines (15) and common practices (51) for BM. This tree was used to define 6 alternative strategies (Table 1). The a priori objective of this paper was to use extant published evidence of efficacy for treatment of brain metastases without attempting to grade or assess the quality or level of evidence for the published treatments. Nevertheless, to aid the reader in assessing the qualities of the studies included, we have provided levels of evidence (based on the Oxford classification) for the studies we reviewed (Table 2).

Efficacy. A PubMed search was conducted using the following search terms: "single," "brain," "metastasis," "treatment," and "management." We limited our search to English language studies and the years 1990 to present. We chose to include studies back to 1990 because that was the year of the seminal randomized study comparing treatment options for BM. Reports involving 5 or fewer patients were excluded. Reports that were limited to patients with multiple BMs were excluded, and as much as possible we tried to limit inclusion of reports that focused solely on solitary brain metastasis treatment. For the Surgery + SRS category, no reports of this kind existed, and we developed a weighting score for these studies detailed below. Reports that did not report local recurrence and survival outcomes were also excluded. Of 1175 results from this PubMed search, 33 studies met criteria for inclusion and were analyzed. The included studies were summarized for type of study, level of evidence, and tumor types included (see Table 3). Because of heterogeneity in design of the various studies, as well as variation in outcome reporting outcomes (recurrence vs. survival, pooled vs. unpooled analysis), we were unable to identify one reasonable outcome by which to measure the variance and heterogeneity (I^2) as is performed in meta-analysis.

Most studies included data from patients with single BM (see Table 2). In reports that included both patients with single, as well as

Table 1. Six Commonly Used Treatment Strategies To Be Examined for Cost-Effectiveness

Treatment Modality	Strategy 1	Strategy 2 a	Strategy 2 b	Strategy 3 a	Strategy 3 b	Strategy 4 a	Strategy 4 b	Strategy 5	Strategy 6 a	Strategy 6 b
First	Surgery	SRS	SRS	WBRT	WBRT	Surg + WBRT	Surg + WBRT	SRS + WBRT	Surgery + SRS	Surgery + SRS
Second	SRS + WBRT	Surgery	WBRT	Surgery	SRS	SRS	Surgery	Surgery	WBRT	SRS
Third		WBRT	Surgery	SRS	Surgery	Surgery	SRS		SRS	WBRT

Strategy 1: Surgery, then SRS + WBRT. Because of the high efficacy of surgery in treating solitary brain metastases, it is generally used as a first-line treatment. If unsuccessful, SRS and/or WBRT can be chosen as a follow-up therapy. Because of the increased efficacy when SRS and WBRT are combined (versus the treatments individually), SRS + WBRT was chosen as the second step in this regimen. A third step was not included in this regimen.

Strategy 2: SRS, then surgery, then WBRT. SRS is used as the first-line treatment in **Strategy 2a** because of its high efficacy. If unsuccessful, surgical resection can be used. If unsuccessful in preventing local or distant recurrence, WBRT can be implemented. Little data exist regarding optimal order of secondary and tertiary therapeutic modalities after failure of a primary or secondary intervention. For this reason, strategies 2—4 include "a" and "b" alternatives, which differ only in the order of the modalities used at the second and third steps.

Strategy 3: Initial WBRT, then surgery, then SRS. In some circumstances, the clinician or patient may elect not to proceed with initial surgical intervention and instead to use WBRT as first-line treatment. If unsuccessful, **Strategy 3a** uses surgery as a second intervention, as it has no delay in efficacy, following an already delayed effect from the WBRT. If unsuccessful, SRS can be administered. **Strategy 3b** reverses the order of SRS and surgery and may be pursued in cases in which there is a strong preference against surgery.

Strategy 4: Surgery + WBRT, then SRS, then surgery. In **Strategy 4a**, surgery and WBRT are given in close succession. Some studies report WBRT before surgery and others report WBRT following surgery, so methods of administering the combination therapy are included in this study of efficacy. SRS can be used after initial failure, as repeat WBRT is generally avoided. In the event of a recurrence, reresection is an option. **Strategy 4b** uses surgical salvage before the SRS option.

Strategy 5: SRS and WBRT, with surgical salvage. When surgery is contraindicated, primary therapy is limited to radiation. Because of the low efficacy of WBRT alone, a combination of SRS and WBRT can be used as a first-line treatment, resulting in a higher rate of efficacy. If unsuccessful, surgery may be considered as a follow-up option, as WBRT would likely not be given again, and as circumstances surrounding the contraindications to surgery may have changed as a result of the first treatment attempt.

Strategy 6: Surgery + SRS boost, with WBRT or SRS salvage. For patients with focal intracranial metastatic disease, some centers are adding SRS boost to the resection cavity and margin following surgical resection. For those patients who do develop recurrence at the primary site or other distant intracranial metastasis, SRS or WBRT may be used as salvage therapy. The two pathways vary only in the order of salvage therapies.

SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.