Title: **Stereotactic Radiosurgical Procedures: Clinical and Cost Effectiveness and Guidelines for Use**

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**Research questions:**

1. What is the clinical effectiveness of stereotactic radiosurgical procedures for patients with head and neck disorders?
2. What is the cost effectiveness of stereotactic radiosurgical procedures for patients with head and neck disorders?
3. Is there evidence for use of stereotactic radiosurgical procedures in other indications?
4. What are the guidelines for use of stereotactic radiosurgical procedures?

**Methods:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and April 2008, except for articles for observational study published between 2007 and April 2008. All the results were limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, clinical guidelines, randomized clinical trial (RCT), and observational studies.

The summary of findings is based only on information contained within the relevant abstracts.

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Results:

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials, observational studies and evidence-based guidelines.

The literature search identified three health technology assessments, eight systematic reviews/meta-analyses, four economic reports, four randomized controlled trials, and eight guidelines. Evidence for the use of stereotactic radiosurgery (SRS) for other indications is provided in the appendix. Twenty-one observational studies published in the last year illustrate numerous other applications for stereotactic radiosurgery including use in non-small cell lung cancer, liver cancer, spinal metastasis, facetogenic back pain, prostate cancer, and multiple sclerosis tremor. Other articles of interest are also included in the appendix.

Overall summary of findings:

Health technology assessments

Three health technology assessments were identified and are summarized below.

The Medical Services Advisory Committee (Canberra, Australia)\(^1\) assessed the safety, effectiveness and cost-effectiveness of the Gamma Knife (GK) for treating cerebral metastases, arteriovenous malformations (AVMs), acoustic neuromas, primary malignant lesions, meningiomas, and pituitary adenomas. They concluded that with minimal comparative evidence, GK radiosurgery appears safe and effective for patients with single cerebral metastases, primary malignant lesions, acoustic neuromas, and pituitary adenomas. However, based on the available evidence no conclusions could be drawn for the effectiveness of GK for meningioma and AVMs. GK was not cost effective when compared with LINAC stereotactic radiosurgery (SRS).\(^1\)

Unidad de Evaluacion de Tecnologias Sanitarias Agencia Lain Entralgo.\(^2\) assessed the efficacy, safety, and costs of the CyberKnife Radiosurgery System (CRS). The quality of the included studies was poor, precluding a definite conclusion for the efficacy and safety of CRS for intracranial and extracranial lesions. However, the authors noted that CRS could be considered as an option for patients with inoperable tumours or tumours unreachable by other stereotactic systems. Fixed costs were found to be more expensive for CRS than conventional SRS.\(^2\)

The Gamma Knife health technology scientific literature review, developed by the Ontario Ministry of Health and Long-Term Care in 2002,\(^3\) assessed the efficacy of GK SRS in the treatment of arteriovenous malformations, acoustic neuroma, cerebral metastases, and trigeminal neuralgia compared with microsurgery and LINAC-based SRS for all conditions except trigeminal neuralgia. There was no evidence to suggest a difference in effectiveness between GK or LINAC-based SRS for the treatment of AVM or acoustic neuroma. LINAC resulted in fewer facial nerve complications than GK. However, microsurgery remained the best overall treatment for these conditions. There was no benefit for SRS compared to whole brain radiotherapy (WBRT) when used as first line radiation treatment for patients with cerebral metastases. SRS was beneficial for recurrent primary brain tumours or metastases following front line radiation therapy. For these tumours, GK provided better control of local regional progression than LINAC, but was also associated with a high level of severe neurotoxicity. GK improved pain in patients with trigeminal neuralgia and side effects were minimal.\(^3\)
Systematic reviews and meta-analyses

Eight systematic reviews/meta-analyses were identified.

The systematic review by Brada and Jankowska\(^4\) compares conventional radiotherapy with stereotactic radiotherapy for pituitary adenomas but no data were provided in the abstract.

Minniti and Brada\(^5\) systematically reviewed the efficacy and toxicity of conventional radiotherapy (RT), fractionated stereotactic radiotherapy (SCRT), and single fraction radiosurgery (SRS) for patients with Cushing’s disease. No studies directly compared the techniques. SRS showed lower efficacy and higher toxicity and was not appropriate treatment for most patients with Cushing’s disease. However, fractionated conventional RT and SCRT were effective treatments for Cushing’s disease not controlled by surgery alone.\(^5\)

Al-Shahi and Warlow\(^6\) systematically reviewed interventions for treating brain arteriovenous malformations in adults. No randomized controlled trials met the inclusion criteria, so conclusions could not be drawn.\(^5\)

Fuentes \etal\(^7\) compared the effectiveness of surgery with radiosurgery (alone or combined with WBRT) for patients with a solitary brain metastasis from successfully treated non-small cell lung cancer. There were no randomized controlled trials (RCTs) meeting the inclusion criteria. The authors felt that including less rigorous trials could result in misleading findings, so no conclusions could be drawn.\(^7\)

Stafinski \etal\(^8\) performed a meta-analysis of RCTs and concurrent cohort studies to assess the effectiveness of SRS alone or combined with WBRT, compared with surgery and/or WBRT for survival, quality of life (QoL), and functional status in patients with brain metastases. Three RCTs and one cohort study were identified. Their findings showed that WBRT combined with SRS improved survival in patients with one brain metastasis. Furthermore, WBRT combined with SRS improved local tumor control and functional independence in all patients.\(^8\)

Mehta \etal\(^9\) systematically reviewed the use of SRS in adult patients with brain metastases. For selected patients with up to three or four small brain metastases (up to 4 cm in diameter), adding SRS to WBRT (SRS boost) improved brain control as compared to WBRT alone. SRS boosts were associated with a small risk of toxicity compared with WBRT alone. However, patients with a single brain metastasis showed improved survival when given a SRS boost. Overall survival was not altered in a select group of patients with newly diagnosed brain metastases when treated with SRS alone. The authors concluded that there was insufficient evidence for the clinical benefits or risks associated with SRS for recurrent or progressive brain metastases.\(^9\)

Tsao \etal\(^10\) systematically reviewed the use of SRS or fractionated SRS in adult patients with malignant glioma. Radiosurgery boost followed by external beam radiotherapy and carmustine did not result in improved survival, local brain control, or QoL, compared with external beam radiotherapy and carmustine alone. Radiosurgery boost was also associated with increased toxicity. The authors concluded that there was insufficient evidence to assess the benefit versus harm associated with fractionated SRS in patients with newly diagnosed or progressive/recurrent malignant glioma.\(^10\)

Lim and Ayiku\(^11\) systematically reviewed the clinical efficacy and safety of GK stereotactic radiosurgery for the treatment of typical trigeminal neuralgia, multiple sclerosis trigeminal
neuralgia, and atypical trigeminal neuralgia. One literature review and 23 case studies were included. There was a lack of studies directly comparing GK stereotactic radiosurgery with other techniques. Available evidence suggests that the GK has similar clinical efficacy (initial and short-term pain relief) to microvascular decompression, percutaneous radiofrequency thermocoagulation rhizotomy, percutaneous glycerol rhizolysis, and percutaneous balloon compression, for patients with typical trigeminal neuralgia. Evidence suggests GK surgery has a low complication risk compared with the other surgical treatments for this group of patients. Limited data for multiple sclerosis and atypical trigeminal neuralgia patients did not allow for meaningful conclusions for these two groups of patients.\textsuperscript{11}

**Economic analyses and cost information**

Four economic evaluations were identified.

Griffiths et al.\textsuperscript{12} compared LINAC radiosurgery with GK radiosurgery. Only a costing evaluation was performed due to limited evidence on comparative effects. GK appeared to be more costly than LINAC. The authors noted that GK may be cost competitive if there is enough patient demand to fully utilize the equipment. Further evidence for increased survival or greater QoL may be required to justify reimbursement for GK surgery.\textsuperscript{12}

The economic analysis by Cho et al.\textsuperscript{13} cannot be summarized, as no data were provided in the abstract.

Ohinmaa\textsuperscript{14} provided cost estimates for the use of GK, CK, and LINAC in Alberta. There was no significant difference in costs for GK and LINAC units, but a CK unit was significantly more expensive than GK or LINAC. From a patient’s perspective, SRS technology was approximately one sixth the cost of microsurgery. Cost for fractionated SRS treatment was significantly higher to the patient and caregiver than for single SRS treatment. From a societal perspective, LINAC and GK would be cost saving, even with only 100 patients per year, although health care resources would not be efficiently used with such low numbers.\textsuperscript{14}

Wellis et al.\textsuperscript{15} analysed direct costs of microsurgical management of intracranial pathology potentially amenable to radiosurgery, using data from 1998 to 1999. Their analysis showed that the primary costs of microsurgery exceeded those of radiosurgery, for established radiosurgical indications.\textsuperscript{15}

**Randomized controlled trials**

Four RCTs were identified.

Muavevic et al.\textsuperscript{16} conducted a study comparing GK surgery with surgery plus WBRT, for patients with a single, small-sized brain metastasis. The analysis was based on 33 patients in the surgery group and 31 patients in the GK group, each with a single, respectable metastasis ≤ 3 cm in diameter. Results showed that GK surgery was less invasive and local tumour control was equivalent to that of surgery plus WBRT treatment. However, distant tumour control was achieved significantly less frequently following GK surgery alone.\textsuperscript{16}

Aoyama et al.\textsuperscript{17} conducted an RCT to determine if WBRT combined with SRS results in improved survival, brain tumour control, functional preservation rate, and frequency of neurologic death. The trial included 132 patients (65 patients receiving WBRT + SRS; 67 patients receiving SRS alone), with one to four brain metastases, each < 3 cm in diameter. The
use of WBRT plus SRS did not improve survival compared with SRS alone. Intracranial relapse occurred considerably more frequently in those patients receiving only SRS, requiring frequent salvage treatment.\(^{17}\)

Andrews \textit{et al.}\(^{18}\) compared patients with one to three newly diagnosed brain metastases receiving WBRT or WBRT followed by SRS boost. The trial randomized 167 patients to WBRT plus SRS boost and 164 patients to WBRT alone. All patients receiving WBRT plus SRS boost showed improved functional autonomy and improved survival for patients with a single unresectable brain metastasis. These findings suggest that this combination treatment could be standard treatment for patients with a single unresectable brain metastasis and should be considered for patients with two or three brain metastases.\(^{16}\)

Souhami \textit{et al.}\(^{19}\) performed a randomized comparison of SRS followed by conventional radiotherapy with carmustine with conventional radiotherapy and carmustine in patients with glioblastoma multiforme. A total of 203 patients were randomly assigned to one of the two groups, with a median follow-up time of 61 months. SRS followed by conventional radiotherapy plus carmustine did not improve the outcome, general QoL, or cognitive functioning in patients with glioblastoma multiforme.\(^{19}\)

\textit{Guidelines and recommendations}

Eight guidelines were identified. Links are provided in the reference list to the full text of the guidelines and only brief summaries of each are given below. It is recommended that the guidelines be viewed directly for complete information on recommendations, benefits, and harms.

A 2006 guideline from the International RadioSurgery Association (IRSA)\(^{20}\) addresses stereotactic radiosurgery for patients with vestibular schwannomas. Radiosurgery with GK, LINACs, or proton beams are among the interventions considered. The guideline includes methodology, description of guideline validation, recommendations with supporting evidence, benefits and harms of implementing the guideline, contraindications, and implementation tools. Recommendations include:

- SRS is typically employed as the first treatment in patients with small to medium size tumours (without symptomatic brainstem compression), and is used to control growth of recurrent or residual tumour after surgical resection. SRS may be especially suitable for preservation of neurological function (cochlear, facial nerve) and tumour growth control.\(^{20}\)
- Patients with large tumours causing symptomatic brainstem compression should be treated with surgical decompression of the tumour. Residual tumour can be treated with SRS.\(^{20}\)

The American College of Radiology (ARC) has published a 2006 revision on its practice guideline for performance of SRS.\(^{21}\) The guideline describes a minimal set of criteria for an SRS quality assurance program, including staffing, quality control, and validation of technique.

Loeffler \textit{et al.} 2006 (ARC)\(^{22}\) updates a previous version of a guideline for single brain metastases. This guideline includes methodology, guideline validation, recommendations with supporting evidence, and implementation tools. Interventions considered are WBRT, SRS, surgical resection, and combination therapy (SRS + SBRT and surgery + WBRT). Recommendations are presented in the form of case studies and a summary.
For patients with no evidence of progressive extracranial disease, surgical resection or SRS is appropriate therapy.\textsuperscript{22}

For patients receiving WBRT, the addition of SRS may increase median survival by several weeks, but can cause potential WBRT toxicity.\textsuperscript{22}

For patients with recurrence of tumours in the treated region or elsewhere in the central nervous system, WBRT, focal radiotherapy, SRS, or surgical resection may be considered. There is no indication of which is the best choice.\textsuperscript{22}

A guideline by Mintz \textit{et al.} 2006 (Cancer Care Ontario)\textsuperscript{23} considers management of single brain metastases. The guideline includes methodology, validation description, recommendations with supporting evidence, and benefits and harms of implementing the guideline. Interventions considered are WBRT, WBRT plus surgery, surgery alone, WBRT with or without SRS, and SRS. Recommendations include:

- Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a single, surgically accessible brain metastasis amenable to complete excision.\textsuperscript{23}
- Postoperative WBRT should be considered for patients having resection of a single brain metastasis.\textsuperscript{23}
- SRS boost following WBRT should be considered for patients with single metastases. There is insufficient evidence to recommend SRS alone as therapy.\textsuperscript{23}

The ACR released a 2006 guideline by Simpson \textit{et al.}\textsuperscript{24} for the follow-up and retreatment of brain metastases. The guideline includes methodology, validation, and recommendations with supporting evidence. Interventions considered are surgical resection, SRS, WBRT, combined therapy (WBRT + SRS, surgery + WBRT, and surgery + SRS), chemotherapy, observation, and follow-up. Recommendations are presented in the form of case studies and a summary, and include:

- WBRT may be the least attractive option for retreatment after initial WBRT.\textsuperscript{24}
- SRS is a viable option if size and number permit.\textsuperscript{24}
- Chemotherapy is occasionally successful for chemosensitive tumours, and repeat surgery may be useful.\textsuperscript{24}

Soffietti \textit{et al.}\textsuperscript{25} published guidelines on the diagnosis and treatment of brain metastases. The guidelines state that SRS should be considered in patients with brain metastases of 3 cm to 3.5 cm in diameter.\textsuperscript{26}

Videtic \textit{et al.} 2006 (ACR)\textsuperscript{26} produced a guideline for treatment of multiple brain metastases. The guideline includes methodology, validation, and recommendations with supporting evidence. Interventions considered are WBRT, radiosensitizer plus WBRT, SRS alone or with WBRT, and surgery. Recommendations are presented in the form of case studies and a brief summary, and include:

- WBRT is an effective palliative treatment for patients with multiple brain metastases.\textsuperscript{26}
- Surgery in this setting remains controversial but may show a survival benefit in selected patients.\textsuperscript{26}
- SRS does not show a survival impact, so careful patient selection is important.\textsuperscript{26}

The National Institute for Clinical Excellence (NICE) published a guideline in 2004\textsuperscript{27} addressing use of the GK for trigeminal neuralgia, based on the systematic review by Lim and Ayiku (2004)\textsuperscript{11}. The guideline supports the use of the GK for trigeminal neuralgia. It includes indications, outline of the procedure, efficacy and safety.\textsuperscript{27}
References summarized:

Health technology assessments

   Summary available: [http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=32007000235](http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=32007000235) (accessed 2008 May 7).

   Summary available: [http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=32006000534](http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=32006000534) (accessed 2008 May 7).
   See English summary p. 6

   Summary available: [http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32004000733](http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32004000733) (accessed 2008 May 7).
   Note: This report was published in 2002

Systematic reviews and meta-analyses


**Economic analyses and cost information**


**Randomized controlled trials**


Guidelines and recommendations


Prepared by:
Karen Cimon, Research Assistant
Kristen Moulton, Research Assistant
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
Appendix – Further information:

Observational studies- other indications


Review articles


Additional references:


