

***Gamma Knife  
radiosurgery***

**January 2006**

MSAC reference 34

**Assessment report**

© Commonwealth of Australia 2006

**ISBN 1 74186 030 X**

**Online ISBN: 1 74186 031 8**

**ISSN (Print) 1443-7120**

**ISSN (Online) 1443-7139**

First printed <add month/year>

Paper-based publications

© Commonwealth of Australia 2006

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

Internet sites

© Commonwealth of Australia 2006

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at <http://www.msac.gov.au/>

Printed copies of the report can be obtained from:

The Secretary  
Medical Services Advisory Committee  
Department of Health and Ageing  
Mail Drop 106  
GPO Box 9848  
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

**MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

This report was prepared by the Medical Services Advisory Committee with the assistance of Mr Luke Marinovich, Project Manager, Ms Alison Griffiths, Research Associate Health Economics and Dr Sarah Lord, Epidemiologist, from the NHMRC Clinical Trials Centre, University of Sydney. The report was edited by Ms Merry Pearson. The report was endorsed by the Minister for Health and Ageing on 3 November 2006.

Publication approval number: 3889

# Contents

---

<b>Executive summary</b> .....	<b>vii</b>
<b>Introduction</b> .....	<b>1</b>
<b>Background</b> .....	<b>2</b>
Gamma Knife radiosurgery.....	2
The procedure .....	2
Intended purpose .....	3
Cerebral metastases .....	3
Primary intracranial cancers .....	7
Benign intracranial neoplasms .....	9
Meningiomas.....	9
Acoustic neuroma .....	10
Pituitary adenoma .....	12
Arteriovenous malformations.....	13
Existing procedures.....	16
Surgery .....	16
Conventional radiotherapy .....	16
Stereotactic radiosurgery .....	17
Comparators.....	17
Marketing status of the technology.....	17
Current reimbursement arrangement .....	17
Potential utilisation of Gamma Knife radiosurgery.....	17
<b>Approach to assessment</b> .....	<b>19</b>
The research questions .....	19
Review of literature .....	21
Search strategy .....	22
Eligibility criteria for studies.....	24
Appraisal .....	26
Data extraction .....	27
Expert advice.....	28
<b>Results of assessment</b> .....	<b>29</b>
Cerebral Metastases .....	29
Arteriovenous Malformations.....	38
Acoustic neuroma.....	43
Primary malignant lesions.....	52
Meningioma.....	59
Pituitary adenoma .....	66
What are the economic considerations?.....	71
Conclusions.....	82
<b>Conclusions</b> .....	<b>84</b>

<b>Recommendation</b> .....	88
<b>Appendix A MSAC terms of reference and membership</b> .....	89
<b>Appendix B Advisory panel</b> .....	91
<b>Appendix C Studies included in the review</b> .....	92
<b>Appendix D Defining the clinical question</b> .....	123
<b>Abbreviations</b> .....	129
<b>References</b> .....	131

## Tables

Table 1	Karnofsky Performance Scale.....	5
Table 2	Symptomatic progression of acoustic neuroma with tumour growth .....	11
Table 3	Spetzler–Martin Scale for evaluating prognosis after surgery .....	14
Table 4	Radiosurgery-based grading scale for evaluating prognosis .....	14
Table 5	Electronic databases searched in this review .....	22
Table 6	Search strategy.....	23
Table 7	Health technology assessment sites searched.....	24
Table 8	Study exclusion criteria .....	25
Table 9	Evidence dimensions.....	27
Table 10	Designations of levels of evidence .....	27
Table 11	Checklist for appraising the quality of randomised controlled studies of interventions .....	28
Table 12	Checklist for appraising the quality of non-randomised studies of interventions .....	28
Table 13	Cerebral metastases: populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews.....	32
Table 14	AVMs: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews .....	41
Table 15	Acoustic neuroma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews .....	47
Table 16	Primary malignant lesions: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews.....	55
Table 17	Meningioma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews .....	62
Table 18	Pituitary adenoma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews .....	68
Table 19	Costing and economic analyses of Gamma Knife radiosurgery published since 1999 .....	73
Table 20	Estimated costs of Gamma Knife and SRS comparators.....	77
Table 21	Cost analysis.....	78
Table 22	Base Case average capital cost per annum .....	79
Table 23	Estimates of Linac radiosurgery usage .....	79
Table 24	Base case average capital equipment costs per patient.....	80

Table 25	Base case incremental cost per patient for Gamma Knife versus adapted Linac.....	80
Table 26	Sensitivity analyses .....	82

## Figures

Figure 1	QUORUM flowchart of study inclusions and exclusions .....	26
----------	---	----

# Executive summary

---

## The procedure

Stereotactic radiosurgery (SRS) involves the use of an external, three-dimensional frame of reference to locate and target intracranial lesions for treatment by a large single fraction of ionising radiation. Radiosurgery is delivered by multiple collimated and convergent beams, with rapid dose fall-off at the target boundary. This technique was originally developed for obliterating small, benign intracranial lesions, with the large dose of irradiation producing focal irreparable damage in cells within the high-dose target volume (Solberg et al 1998). Target destruction occurs due to direct cell damage or disruption of blood supply.

Gamma Knife radiosurgery is a method for delivering stereotactic irradiation. It has been described as a four-step procedure:

1. application of the stereotactic frame
2. acquisition of images
3. dose planning
4. delivery of radiation (Elekta Instruments 2000; Lindquist 1995).

A stereotactic head frame is used for target localisation and head support during treatment. The frame is fixed to the patient's head using screws at four sites. The frame provides the basis for determining target coordinates and is used to immobilise and position the patient's head within the collimator helmet during treatment. Dose planning is based on stereotactic images, which are usually generated by angiography, computed tomography (CT) or magnetic resonance imaging (MRI). A series of images is taken and electronically transferred to the treatment planning system. The target is localised in three dimensions and its  $x$ ,  $y$  and  $z$  coordinates are determined. Once the images have been imported into the treatment planning system, the lesion is outlined. Multiple isocentres are often placed on the lesion in two and three-dimensional views to achieve a dose distribution which conforms to lesion geometry. For the actual radiation delivery, the patient is placed on a moveable couch with their head positioned in the appropriate collimator helmet (according to coordinates). The stereotactic frame is used to position the lesion at the focal point of the 201 cobalt beams. The couch moves into the gamma unit to initiate treatment, with a typical treatment session lasting approximately 40 to 60 minutes, depending on the complexity of the treatment plan. The couch moves out of the gamma unit at the end of treatment (Elekta Instruments 2000; Lindquist 1995).

## Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on Gamma Knife radiosurgery. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

## MSAC's assessment of Gamma Knife radiosurgery

### Clinical need

#### Cerebral metastases

Australian data on the annual incidence of brain metastases are not available. However, based on estimates of a 20 to 40 per cent incidence of cerebral metastases in all cancer cases, an annual incidence of 17,680 to 35,359 cases of cerebral metastases can be estimated from 88,398 primary cancers (excluding non-melanocytic skin cancers) reported to state and territory cancer registries in 2001 (Australian Institute of Health and Welfare—AIHW—2004). However, it is likely that this annual incidence is an overestimate due to the fact that the base number of primary cancers from which it was derived includes tumours that infrequently result in cerebral metastases. A more conservative annual incidence estimate of between 5,871 and 11,742 cases can be derived from the figure of 29,356 cases of primary melanoma and lung, breast and colorectal cancers.

Not all patients with a diagnosis of cerebral metastases will require, or be eligible for, treatment, depending on severity of symptoms and extent of systemic disease. Between July 2003 and June 2004, 3,688 admissions to Australian public and private hospitals recorded a principal diagnosis of secondary malignancies of brain or cerebral meninges (International Classification of Diseases, 10th Revision—ICD 10-AM—code C79.3) at separation (including discharges, transfers, deaths or changes in care type).

Approximately twothirds of patients were between 55 and 79 years of age. The average length of hospital stay was 9.9 days. These figures may include multiple admissions for a single patient and do not include patients receiving radiotherapy as outpatients. Of all patients with cerebral metastases currently treated by surgery or radiotherapy, only a proportion of those with up to four cerebral metastases will be eligible for stereotactic radiosurgery.

#### Arteriovenous malformations

A population-based epidemiological study from the United States has estimated an annual detection rate of 1.34 per 100,000 population, of which approximately half may

present with haemorrhage (Stapf et al 2003). Based on this figure, approximately 270 new cases of cerebral AVM may be expected to be detected in Australia each year.

Between July 2003 and June 2004, 318 hospital separations were recorded in Australia with a principal diagnosis of cerebral AVM (Q28.2; AIHW 2005a). Most patients were aged between 30 and 59 years (147/318, or 46%, of admissions); however, patient age was broadly distributed, with 117 admissions for patients less than 30 years and 54 admissions for patients aged 60 years or older. The average length of hospital stay was 7.5 days. Over the same period, 181 hospital procedures were performed to excise an intracranial AVM (ICD-10-AM 39803-00; AIHW 2005b). The proportion of those admissions and procedures that may be eligible for SRS can not be determined.

### **Acoustic neuroma**

Acoustic neuromas account for approximately 6 per cent of primary intracranial tumours, with an annual incidence of 0.3 to 1.3 per 100,000 individuals reported internationally (Lin et al 2005; Tos et al 2004). Based on these figures, up to 265 new cases of acoustic neuroma a year may be expected in Australia. Findings from a large MRI series in the United States estimated the prevalence of incidental acoustic neuromas at 2 per 10,000 individuals (Lin et al 2005).

Between July 2003 and June 2004, 388 hospital separations were recorded in Australia with a principal diagnosis of benign cranial nerve tumour. Most of these patients were aged 45 years or older and the average length of hospital stay was 9.3 days. Over the same period, 286 hospital procedures for decompression of cranial nerves, including 49 cases for decompression of the facial nerve (ICD-10AM 41569-00 49) and 237 cases for decompression of other cranial nerves (ICD-10-AM 39112-00; AIHW 2005b). The proportion of those admissions and procedures that were due to acoustic neuroma and may be eligible for SRS can not be determined.

### **Primary malignant lesions**

In 2001, 1,348 new cases of primary brain cancer and 73 new cases of cancers of the meninges and other central nervous system sites were reported (AIHW 2004). These figures correspond to an age-standardised annual incidence of 7.3 cases per 100,000 population.

Incidence rates were highest for individuals aged between 65 years and 84 years (22–24 cases per 100,000 in 2001; AIHW 2004). In the childhood years, incidence rates were highest for those aged 0 to 4 years (4.1 cases per 100,000 in 2001; AIHW 2004). The average annual age-standardised mortality rate was reported as 5.6 per 100,000 over the period 1998 to 2002, with a median age at death of 63 years (AIHW 2004).

Overall, 4,384 hospital separations were recorded between July 2003 and June 2004 for patients with a primary diagnosis of malignant neoplasm of the brain, with an average length of stay of 11.3 days (ICD-10AM code C71). Expert opinion estimates that approximately 25 per cent of these patients (1,096) were eligible for SRS.

### **Meningioma**

Meningiomas account for between 14 to 18 per cent of all intracranial neoplasms (Nakamura et al 2003). A population-based epidemiological study from the United States estimated an incidence of symptomatic disease in 2 per 100,000 population per year, with

a higher figure when patients with incidental and autopsy diagnosis are included (Radhakrishnan et al 1995).

Patients may present with seizures, headaches and neurological deficits, including of the cranial nerves, depending on the site of the tumour (Black 1995).

Between July 2003 and June 2004, 1,095 hospital separations were recorded in Australia with a principal diagnosis of benign meningioma (ICD-10AM code D32; AIHW 2005a). Most of these patients (65%) were aged between 45 and 74 years. The average length of hospital stay was 10.3 days. Over the same period, 774 hospital procedures to remove tumours from cerebral meninges were performed in Australia (ICD-10-AM 39112-00; AIHW 2005b). The proportion of these admissions and procedures that were due to benign meningioma can not be determined.

### **Pituitary adenoma**

Pituitary adenomas account for between 10 and 20 per cent of all primary brain tumours (Sheehan et al 2005). A population-based epidemiological study from the United States has estimated the incidence of symptomatic presentations at 2.4 per 100,000 population per year for pituitary adenomas (Radhakrishnan et al 1995). Based on these figures, approximately 490 new symptomatic cases of pituitary adenomas a year may be expected in Australia. This figure is higher for patients with subclinical disease. A systematic review and meta-analysis has estimated the prevalence of pituitary adenomas at 16.7 per cent based on radiological and autopsy findings (Ezzat et al 2004).

Between July 2003 and June 2004, 522 hospital separations were recorded in Australia with a principal diagnosis of pituitary adenoma (ICD-10-AM D35.2; AIHW 2005a). Most of those patients were aged between 40 and 69 years of age and the average length of hospital stay was 7.0 days. Over the same period, 483 hospital procedures were performed involving total or partial removal of the pituitary gland (ICD-10-AM 39715-00, 39715-01, 90048-00, 90048-01, 90048-02; AIHW 2005b). The proportion of these admissions and procedures that may be eligible for SRS is not known.

## **Safety**

### **Summary**

There was a lack of comparative evidence for conclusions about the relative safety of Gamma Knife radiosurgery versus alternative treatments for the indications reviewed.

Gamma Knife radiosurgery appears to result in a lower rate of medium-term treatment-related complications and procedural mortality than surgery for the treatment of acoustic neuroma. The addition of stereotactic radiosurgery to whole brain radiotherapy (WBRT) for the treatment of cerebral metastases may result in a slightly increased risk of serious radiation-related toxicity. Safety findings for each of the indications are discussed in the following sections.

### **Cerebral metastases**

Level II evidence suggests that the addition of SRS to WBRT results in a slightly increased risk of serious radiation-related toxicity compared with WBRT alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. The present

review is unable to update the conclusions of the previous MSAC assessment in terms of the relative safety of Gamma Knife and linear accelerator (Linac) radiosurgery, and there were no studies on which to base conclusions regarding the comparative safety of Gamma Knife and CyberKnife radiosurgery. The comparative safety of these different types of SRS remains uncertain. Similarly, no conclusions are possible regarding the comparative safety of Gamma Knife radiosurgery and surgery plus WBRT.

### **Arteriovenous malformations**

In the absence of additional comparative evidence since the completion of MSAC's previous assessment of Gamma Knife radiosurgery, this review is unable to update those conclusions. Event rates appear to be similar in patients treated with Gamma Knife and Linac SRS, but methodological limitations, patient selection biases and inconsistencies in reporting adverse events prevented meaningful comparisons between the safety of Gamma Knife and Linac SRS and traditional surgery.

### **Acoustic neuroma**

There is Level III-2 and III-3 evidence that Gamma Knife radiosurgery appears to result in a lower rate of medium-term treatment-related complications and procedural mortality than does surgery. However, methodological limitations of these studies preclude conclusions regarding the magnitude of that effect. The relative long-term safety of Gamma Knife radiosurgery and surgery could not be assessed. There was no evidence on which to base a comparison between Gamma Knife and other forms of SRS (Linac and CyberKnife).

### **Primary malignant lesions**

There is Level II evidence that the addition of SRS to conventional radiotherapy plus chemotherapy (with BCNU, a proprietary form of the drug carmustine) results in a slightly increased risk of late Grade 3 radiation-related toxicity compared with external-beam radiotherapy (EBRT) and BCNU alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. No conclusions about the relative safety of Gamma Knife and alternative forms of SRS (Linac and CyberKnife) are possible.

### **Meningioma**

Due to methodological limitations of the included Level III-2 studies, it is not possible to draw definitive conclusion regarding the relative safety of Gamma Knife radiosurgery and surgery. Complications after Gamma Knife radiosurgery tend to be transitory in the short-to-medium term, but inadequate follow-up precludes conclusions about long-term safety. A lack of comparative evidence further precludes conclusions regarding the relative safety of Gamma Knife radiosurgery and conventional radiotherapy (alone or combined with surgery), and other forms of SRS (Linac, CyberKnife).

### **Pituitary adenoma**

Definitive conclusions about the relative efficacy of Gamma Knife radiosurgery and alternative treatments are not possible. Level III-2 evidence suggests that complications after Gamma Knife radiosurgery in addition to surgery are rare in the short-to-medium term in terms of mortality, pituitary dysfunction or worsening visual function, but long-term safety is uncertain. The methodological limitations of this evidence preclude conclusions about the comparative safety of Gamma Knife radiosurgery and surgery.

There were no comparative studies on which to base conclusions on the relative safety of Gamma Knife radiosurgery and conventional radiotherapy (with or without surgery), or different forms of SRS (Gamma Knife, Linac, CyberKnife).

## **Effectiveness**

### **Summary**

There is Level II evidence for a small increase in survival for patients with single metastases treated by SRS plus WBRT compared with WBRT alone, but this increase was not evident in patients with multiple metastases. There was Level II evidence for no difference in survival, neurological function or quality of life for patients with primary lesions treated by SRS in addition to EBRT, surgery and chemotherapy, compared with these treatments without SRS. Observational evidence suggests that there is no difference in survival for patients with cerebral metastases or primary malignancies treated by Gamma Knife versus Linac-based SRS.

Due to the quality of the evidence regarding acoustic neuroma, the conclusions from MSAC's previous assessment cannot be advanced. Gamma Knife radiosurgery may be comparable to surgery for controlling acoustic neuroma. Gamma knife radiosurgery may also improve quality of life, hearing preservation and facial function in selected patients with acoustic neuroma for whom surgery is not indicated, but the magnitude of benefit is uncertain. There is also Level III-2 evidence that patients with residual non-functioning pituitary adenoma after surgery benefit from Gamma Knife radiosurgery in terms of tumour progression compared with patients who are observed after surgery. However, there is no evidence comparing the rates of tumour progression in such patients undergoing radiotherapy after surgery.

The methodological quality of the evidence for meningioma prevents conclusions regarding the comparative effectiveness for Gamma Knife radiosurgery. There were no comparative studies addressing the indication of arteriovenous malformations. Gamma Knife radiosurgery was unable to be compared with CyberKnife across all indications due to a lack of comparative evidence. CyberKnife radiosurgery is not available in Australia.

The conclusions for each indication are further discussed in the following sections.

### **Cerebral metastases**

There is Level II evidence that the addition of SRS to WBRT does not improve or decrease overall survival compared to WBRT alone in patients with multiple cerebral metastases. However, there is Level II evidence of a small but statistically significant improvement in survival (1.6 months) when SRS is used as a boost to WBRT in patients with single metastases. SRS may lead to improvements in tumour control and patient performance in patients with up to three metastases; however, definitive conclusions are not possible.

There is Level III-2 evidence that there is no difference in overall survival between patients with multiple cerebral metastases treated by Gamma Knife versus Linac-based radiosurgery (in addition to WBRT).

There were no studies on which to base conclusions regarding the relative effectiveness of Gamma Knife and CyberKnife SRS. Similarly, no conclusions are possible concerning a comparison between Gamma Knife radiosurgery and observation.

### **Arteriovenous malformations**

In the absence of comparative studies, this assessment is unable to update the findings of the previous MSAC review and the systematic review conducted by Hailey (2002). Gamma Knife radiosurgery should continue to be regarded as a complimentary approach to surgery in patients with surgically inaccessible lesions or those with co morbidities which preclude surgical intervention. There is no evidence on which to base conclusions about the relative effectiveness of Gamma Knife, Linac and CyberKnife SRS for the treatment of AVM.

### **Acoustic neuroma**

Due to the methodological quality of the Level III-2 and Level III-3 evidence identified by the current review, it remains difficult to draw firm conclusions regarding the relative effectiveness of Gamma Knife radiosurgery compared with surgery for the treatment of acoustic neuroma. It is not possible to advance the conclusions reported in the previous MSAC assessment. Gamma Knife radiosurgery appears to offer similar outcomes in terms of tumour control to those from surgery. Gamma Knife radiosurgery may offer some benefits in terms of quality of life, hearing preservation and facial function in selected patient groups for whom surgery is not indicated, but in the absence of randomised controlled studies there is considerable uncertainty in specifying the magnitude of benefit. No comparison between Gamma Knife and Linac-based radiosurgery was possible, and hence the tentative conclusion reported in the previous MSAC review of little difference between the modalities is still applicable. Further, there were no studies on which to base conclusions on the comparative effectiveness of Gamma Knife and CyberKnife radiosurgery.

### **Primary malignant lesions**

There is Level II evidence that the addition of SRS to EBRT, surgery and chemotherapy does not improve or decrease survival, neurological function or quality of life compared with EBRT, surgery and chemotherapy alone in patients with primary malignant lesions (glioblastoma multiforme). There is Level III-2 evidence that there is no difference in overall survival between patients treated by Gamma Knife versus Linac-based radiosurgery (in addition to surgery, EBRT and chemotherapy). No studies were identified that addressed the relative effectiveness of Gamma Knife and CyberKnife radiosurgery, and hence no conclusions may be drawn regarding comparisons between these forms of SRS.

### **Meningioma**

The methodological quality of the Level III-2 evidence identified by the current review prohibits meaningful conclusions regarding the comparative effectiveness of Gamma Knife radiosurgery (alone or in combination with surgery) and surgery in patients with meningiomas. Similarly, conclusions comparing the effectiveness of Gamma Knife radiosurgery and conventional radiotherapy (with or without surgery), observation, or other forms of SRS (Linac or CyberKnife) are not possible given the lack of comparative studies.

## **Pituitary adenoma**

There is Level III-2 evidence that patients with residual non-functioning pituitary adenoma after surgery benefit from Gamma Knife radiosurgery in terms of tumour progression, compared with patients who are observed after surgery. However, there is no evidence comparing the rates of tumour progression in such patients undergoing radiotherapy after surgery. The methodological quality of the evidence does not permit conclusions regarding the relative effectiveness of Gamma Knife radiosurgery in terms of post-treatment hormone function. No comparisons between Gamma Knife radiosurgery and radiotherapy (either alone or in combination with surgery) or observation alone are possible. Similarly, this review is unable to address comparisons on effectiveness between Gamma Knife and other forms of SRS (Linac and CyberKnife).

## **Cost effectiveness**

A partial economic costing indicates that an adapted Linac unit would provide the least costly method of SRS treatment in Australia. The base case estimate for the cost per treatment for Gamma Knife radiosurgery was estimated at \$3,757 compared to a range of \$960 to \$3,549 for an adapted Linac unit, depending on the proportion of the standard Linac unit capital costs attributed. However, this analysis does not take into account potential differences in the effectiveness of Gamma Knife, Linac and CyberKnife SRS and the results are sensitive to variations in assumptions. Further evidence about the effectiveness of Gamma Knife radiosurgery versus alternatives such as adapted Linac systems is required in order to undertake a full economic analysis.

## **Recommendation**

Gamma Knife radiosurgery is safe, appears to be effective, but is not cost effective when compared with Linac stereotactic radiosurgery.

MSAC recommends that current funding arrangements should not be changed.

- The Minister for Health and Ageing accepted this recommendation on 3 November 2006

# Introduction

---

The Medical Services Advisory Committee (MSAC) has reviewed the use of Gamma Knife radiosurgery, which is a therapeutic technology for treating serious intracranial lesions. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for Gamma Knife radiosurgery for the indications of primary and metastatic intracranial cancers, arteriovenous malformations, and benign intracranial lesions (acoustic neuroma, meningioma and pituitary adenoma). The evidence summarised in this report updates the previous assessment of Gamma Knife radiosurgery conducted by MSAC in 2001.

# Background

---

## Gamma Knife radiosurgery

This evaluation was undertaken in response to an application for assessment of Gamma Knife radiosurgery to receive specific reimbursement under the Australian Medicare Benefits Scheme (MBS). Stereotactic radiosurgery is currently eligible for funding under MBS (Australian Government Department of Health and Aged Care 2004). All currently operating facilities in Australia are modified linear accelerators.

Stereotactic radiosurgery involves the use of an external, three-dimensional frame of reference to locate and target intracranial lesions for treatment by a large single fraction of ionising radiation. Radiosurgery is delivered by multiple collimated and convergent beams, with rapid dose fall-off at the target boundary. This technique was originally developed for obliterating small, benign intracranial lesions, with the large dose of irradiation producing focal irreparable damage in cells within the high-dose target volume (Solberg et al 1998). Target destruction occurs due to direct cell damage or disruption of blood supply.

There are three potential methods for delivering stereotactic irradiation:

1. linear accelerator (Linac)
2. Gamma Knife
3. charged-particle irradiation.

Fractionated stereotactic radiotherapy can also be performed using Linac and Gamma Knife delivery systems. This technique divides the radiation dose over multiple treatment sessions similar to conventional radiotherapy treatments. It has been proposed that fractionated dosing allows preferential repair of radiation-induced sublethal damage by normal surrounding tissue, compared with the abnormal target. This allows a differential effect to enable treatment and can be used to treat lesions located in critical areas of the brain or close to critical structures which were previously considered unsuitable for stereotactic radiosurgery.

CyberKnife is a recent evolution of Linac technology which involves the delivery of radiation via a robotic system (Accuray 2005). The system does not require a head frame, and unlike Gamma Knife and Linac-based radiosurgery, CyberKnife can more easily treat lesions in areas of the body other than the head. The system corrects for motion effects due to respiration or other patient movement in real time, and it has therefore been proposed that CyberKnife is more accurate than other forms of radiosurgery (Accuray 2005).

## The procedure

Gamma Knife radiosurgery has been described as a four-step procedure:

1. application of the stereotactic frame
2. acquisition of images

3. dose planning
4. delivery of radiation (Elekta Instruments 2000; Lindquist 1995).

A stereotactic head frame is used for target localisation and head support during treatment. The frame is fixed to the patient's head using screws at four sites. The frame provides the basis for determining target coordinates and is used to immobilise and position the patient's head within the collimator helmet during treatment. Dose planning is based on stereotactic images, which are usually generated by angiography, computed tomography (CT) or magnetic resonance imaging (MRI). A series of images is taken and electronically transferred to the treatment planning system. The target is localised in three dimensions and its  $x$ ,  $y$  and  $z$  coordinates are determined. Once the images have been imported into the treatment planning system, the lesion is outlined. Multiple isocentres are often placed on the lesion in two and three-dimensional views to achieve a dose distribution which conforms to lesion geometry. For the actual radiation delivery, the patient is placed on a moveable couch with their head positioned in the appropriate collimator helmet (according to coordinates). The stereotactic frame is used to position the lesion at the focal point of the 201 cobalt beams. The bed moves into the gamma unit to initiate treatment, with a typical treatment session lasting approximately 40 to 60 minutes, depending on the complexity of the treatment plan. The couch moves out of the gamma unit at the end of treatment (Elekta Instruments 2000; Lindquist 1995).

## Intended purpose

Gamma Knife is intended to treat malignant and benign intracranial conditions. This report provides an assessment of six specific indications:

1. cerebral metastases
2. arteriovenous malformations (AVMs)
3. benign intracranial tumours
  - i. acoustic neuroma
  - ii. meningioma
  - iii. pituitary tumours
4. primary malignant intracranial tumours.

These indications were selected by the advisory panel to reflect the most common potential uses for Gamma Knife radiosurgery. Trigeminal neuralgia and functional neurosurgery in general were identified as other potential applications for Gamma Knife technology; however, it was the advisory panel's opinion that those conditions are unlikely to result in large patient numbers in Australia, and that there is no extensive evidence base for these applications. Therefore, this assessment will address the indications listed. A description of the epidemiology, burden of disease and current treatment options for each of these conditions is described in the following sections.

## Cerebral metastases

Many primary cancers are associated with the development of secondary cancers in the brain (cerebral metastases). Cancer can spread to the brain via blood vessels or, very

rarely, by direct extension from adjacent extracranial cancers. The most common primary cancer types associated with cerebral metastases in adults are lung, breast, colorectal, melanoma and renal cell, with the highest rate for those aged 55 to 65 years (Patchell 2003; Westphal, Heese, & de Wit 2003).

Cerebral metastases occur in about 20 to 40 per cent of all cancer patients (Patchell 2003). This figure may be increasing due to the use of advanced imaging techniques such as MRI for early detection and improved treatment regimens leading to prolonged patient survival. Approximately 70 per cent of cerebral metastases present as multiple lesions (Patchell 2003).

### **Clinical need/burden of disease**

Patients with cerebral metastases may present with headaches, seizures, lethargy, and changes in personality, mental capacity and emotional stability. Other symptoms, such as sensory problems or weakness, may occur according to the site of the metastasis. Cerebral metastases may also be found in asymptomatic patients undergoing staging tests for a known primary cancer. Treatment is generally undertaken for symptom relief (palliation).

The outcome for untreated patients is poor, with a mean survival of approximately one month after diagnosis (Patchell 2003). Patients may also die of increasing intracranial pressure due to cerebral disease or other organ failure as a result progressive systemic cancer spread.

Australian data on the annual incidence of brain metastases are not available. However, based on estimates of a 20 to 40 per cent incidence of cerebral metastases in all cancer cases, an annual incidence of 17,680 to 35,359 cases of cerebral metastases can be estimated from 88,398 primary cancers (excluding non-melanocytic skin cancers) reported to state and territory cancer registries in 2001 (AIHW 2004). However, it is likely that this annual incidence is an overestimate, due to the fact that the base number of primary cancers from which it was derived includes tumours that infrequently result in cerebral metastases. A more conservative annual incidence estimate of between 5,871 to 11,742 cases can be derived from the figure of 29,356 cases of primary melanoma, lung, breast and colorectal cancer.

Not all patients with a diagnosis of cerebral metastases will require, or be eligible for, treatment depending on severity of symptoms and extent of systemic disease. Between July 2003 and June 2004, 3,688 admissions to Australian public and private hospitals recorded a principal diagnosis of secondary malignancies of brain or cerebral meninges (ICD 10-AM, code C79.3) at separation (includes discharges, transfers, deaths or changes in care type). Approximately two-thirds of those patients were between 55 and 79 years of age. The average length of hospital stay was 9.9 days. These figures may include multiple admissions for a single patient and do not include patients receiving radiotherapy as outpatients. Of all patients with cerebral metastases currently being treated by surgery or radiotherapy, only a proportion of those with up to four cerebral metastases will be eligible for stereotactic radiosurgery.

### **Classification of patient performance status**

Classification of patient performance status is used to predict prognosis and guide treatment decisions. It is also used as an outcome measure in studies assessing the

effectiveness of treatment. The Karnofsky Performance Scale (KPS) is the most commonly used tool and has excellent reliability and strong predictive validity in patients with cancer (Mor et al 1984). The KPS is described in Table 1.

**Table 1 Karnofsky Performance Scale**

	Patient performance	Score
A Able to carry on normal activity and to work; no special care needed.	Normal no complaints; no evidence of disease.	100
	Able to carry on normal activity; minor signs or symptoms of disease.	90
	Normal activity with effort; some signs or symptoms of disease.	80
B Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	Cares for self; unable to carry on normal activity or to do active work.	70
	Requires occasional assistance, but is able to care for most of his personal needs.	60
	Requires considerable assistance and frequent medical care.	50
C Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Disabled; requires special care and assistance.	40
	Severely disabled; hospital admission is indicated although death not imminent.	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

Adapted from Karnofsky, D., et al 1948. 'The use of nitrogen mustards in the palliative treatment of carcinoma,' *Cancer*, 1, 634–656.

## Standard treatment

Standard treatments for cerebral metastases include corticosteroids, external beam whole brain radiotherapy (WBRT), radiosurgery and surgery. The role of chemotherapy is not well established but may have a role for chemo-sensitive primary cancers (Westphal, Heese & de Wit 2003).

## Corticosteroid treatment

Corticosteroids (primarily dexamethasone) are used to reduce tissue swelling and intracranial pressure to palliate symptoms. Clinical improvement in neurological function may be observed within 24 to 48 hours. They are reported to extend median patient survival by approximately four to eight weeks over no treatment (Horton, Baxter & Olson 1971; Weissman 1988). Prolonged use of corticosteroids is associated with side effects, but patients generally die from progressive neurological disease (Horton, Baxter & Olson 1971; Kurtz et al 1981; Markesbery et al 1978; Patchell 1991; Zimm et al 1981).

## Surgery

Microsurgery is the standard treatment for patients with a single surgically accessible cerebral metastasis (Patchell 2003). For the purposes of this report, 'surgery' will be used to denote 'microsurgery'. It is imperative for patients with a life threatening mass effect who are fit for surgery. Surgery is also indicated for patients with an unknown primary cancer.

As outlined in the previous MSAC review, two randomised controlled trials (RCTs) have shown a significant survival benefit for a combination of surgery and WBRT in patients with single cerebral metastases (median survival 9 to 10 months for surgery plus WBRT versus 4 to 6 months for WBRT alone; Patchell et al 1990; Vecht et al 1993). A third trial failed to show a similar benefit (Mintz et al 1996). These conflicting results have been attributed to a higher proportion of patients with disseminated systemic disease and lower performance scores in the study reported by Mintz et al (1996). Meta-analysis of these data indicated a trend favouring surgery and WBRT to reduce deaths due to neurological causes (OR 0.57, 95% CI 0.29–1.10,  $p = 0.09$ ) in patients with single brain metastases without increasing adverse events (Hart et al 2004). A fourth trial demonstrated a significant benefit in patient performance scores and median time to death due to neurological causes in patients treated with complete surgical resection of a single cerebral metastases plus WBRT versus surgery alone (115 weeks versus 81 weeks,  $p = 0.003$ ); however, this effect was not associated with a difference in overall survival time (Patchell et al 1998).

Factors associated with a favourable response following surgery include controlled primary cancer, the absence of other sites of metastatic disease and good patient performance scores.

Potential post-operative complications include further deterioration of neurological function (estimated in 5% of cases) and local complications such as haematoma and infection. General post-operative complications occur in about 8 to 10 per cent of patients and include pneumonia, deep venous thrombosis and pulmonary embolism. Surgical mortality rates of between 0 and 10 per cent have been reported in the literature for patients with cerebral metastases by surgery over the last 10 years (Lang & Sawaya 1998).

No randomised trials have assessed the effect of surgery for removing two or more metastases. Alternative treatments for this patient group include WBRT, SRS or a combination of WBRT and SRS.

### **Whole brain radiotherapy**

WBRT is the standard treatment for patients with multiple cerebral metastases (more than four lesions) who are not eligible for surgery or radiosurgery. Observational evidence indicates that it reduces patient symptoms and prolongs survival more effectively than steroids alone. Median survival following WBRT has been estimated at three to six months (Patchell 2003). Treatment usually involves 7 to 15 day courses of radiotherapy. Trials have not yet established an optimal treatment dose and schedule (Patchell 2003).

Factors associated with a favourable response following WBRT include Karnofsky performance scores greater or equal to 70 per cent; absent or controlled primary tumours; patients younger than 60 years; and no other sites of metastatic disease (Patchell 2003). Large retrospective studies have reported that most patients treated with WBRT die of progressive systemic cancer rather than brain metastases.

The most common treatment complication is temporary loss of hair (alopecia). Patients may also experience nausea and vomiting, skin changes and worsening of neurological symptoms due to short-term swelling at the treatment site. One randomised trial has indicated that the 30 day mortality rate following WBRT is the same as that for surgery

(4% for both WBRT and surgery, Patchell et al 1998). Potential long-term side effects are less relevant due to the short median survival for this population. Dementia has been reported in up to 11 per cent of patients surviving longer than 12 months after treatment; however, this figure is based on patients treated with large radiation fractionation schedules that are no longer used and may overestimate the harms of current radiotherapy schedules (Patchell 2003).

### **Stereotactic radiosurgery**

Stereotactic radiosurgery (SRS) is currently used as an alternative to surgery in patients with metastases of up to 3 cm that are surgically inaccessible or sited in regions of the brain related to motor or sensory function (referred to as the 'eloquent cortex').

The previous MSAC report (2001) identified one RCT comparing a combination of SRS and WBRT to WBRT alone for patients with multiple cerebral metastases (Kondziolka et al 1999). This trial reported improved local tumour control but no survival benefit; however, this evidence was limited by the small sample size (27 patients) and inadequate randomisation method used. No trials were identified that directly compared SRS with surgery in patients eligible for both treatments. This report presents an update of the available evidence.

Potential complications following SRS include radiation injury and necrosis. Radiation necrosis has been reported in approximately 5 per cent of patients following SRS in two single-centre studies (Brown et al 2002, 41 patients; Petrovich et al 2002, 458 patients). The consequences of radiation-induced swelling and necrosis largely depend on the site of the cancer.

## **Primary intracranial cancers**

Most primary brain cancers arise from the glial cells that surround and support nerve cells (referred to as gliomas). Primary brain cancer is relatively rare in adults, but it is the most common solid cancer in children under the age of 15 years (AIHW & AACR 2004). Common tumour types vary in these different age groups. In adults, onset is generally between age 50 to 60 years and anaplastic astrocytomas, glioblastomas, meningiomas and other mesenchymal tumours are most common (Levin, Leibel, & Gutin 2001). In children, cerebellar astrocytomas, medulloblastomas, ependymomas and brain stem gliomas are most common.

Exposure to vinyl chloride is associated with an increased risk of glioma in adults. Familial syndromes such as neurofibromatosis types I and II, von Hippel-Lindau disease and tuberous sclerosis are also associated with primary intracranial cancers (Levin et al 2001).

### **Clinical need/burden of disease**

Similar to the clinical presentation of cerebral metastases, patients with primary intracranial cancers may present with general symptoms such as headaches, seizures, lethargy, nausea, vomiting and changes in personality, mental capacity, or emotional stability. Localising symptoms such as sensory problems or weakness may also occur.

Treatment is given with curative intent and prognosis varies according to the histologic type, grade, postoperative size and extent of the tumour, patient age and performance status. Most children will survive five years from diagnosis, with the possibility of cure in some (NIH 2005). The prognosis in adults varies widely by tumour histology and grade; five-year survival for low-grade cancers has been reported at approximately 65 per cent (Karim et al 2002) compared to approximately 25 per cent survival at two years for high-grade tumours (Stupp et al 2005).

In 2001, 1,348 new cases of primary brain cancer and 73 new cases of cancers of the meninges and other central nervous system sites were reported (AIHW 2004). These figures correspond to an age-standardised annual incidence of 7.3 cases per 100,000 population.

Incidence rates were highest for individuals aged between 65 years and 84 years (22–24 cases per 100,000 in 2001, AIHW 2004). In the childhood years, incidence rates were highest for those aged 0 to 4 years (4.1 cases per 100,000 in 2001, AIHW 2004). The average annual age-standardised mortality rate was reported as 5.6 per 100,000 over the period 1998 to 2002, with a median age at death of 63 years (AIHW 2004).

Overall, 4,384 hospital separations were recorded between July 2003 and June 2004 for patients with a primary diagnosis of malignant neoplasm of the brain with an average length of stay of 11.3 days (ICD-10AM, code C71). Expert opinion estimates that approximately 25 per cent of these patients (1,096) were eligible for SRS.

Despite ranking as the 14th most common cancer in Australia, cancer of the brain and nervous system ranks as the fourth highest cancer in terms of the number of person-years of life lost (16,968) due to childhood onset brain cancers (AIHW 2004).

## **Standard treatment**

### **Surgery and conventional radiotherapy**

Standard treatment is individualised to the patient according to the histology and location of the cancer. Surgery is generally performed for biopsy, with partial or total resection followed by conventional radiotherapy. Patient factors associated with a favourable prognosis following surgery include age under 40 years and good patient performance scores. The potential complications of these treatments are similar to those described for cerebral metastases. Radiation necrosis may also be evident since the radiation dose for primary lesions is approximately twice that delivered to cerebral metastases.

Surgical excision allows a histological diagnosis and aims to relieve raised intracranial pressure and associated symptoms to improve quality of life, and in some cases to prolong survival. Total resection is rarely achieved due to tumour infiltration.

Conventional radiotherapy is also indicated for cancers that are surgically inaccessible or where removal of the tumour mass may compromise neurological function.

### **Chemotherapy**

A recent multi-centre RCT of 573 patients with high-grade glioblastomas has demonstrated a small survival benefit for chemotherapy with temozolomide plus conventional radiotherapy (median survival 14.6 months, 95% CI: 13.2–16.8) versus radiotherapy alone (median survival 12.1 months, 95% CI: 11.2–13.0) (Stupp et al 2005). Temozolomide is currently the standard treatment for glioblastomas in Australia.

### **Stereotactic radiosurgery**

Radiosurgery with or without conventional radiotherapy has been proposed as an alternative treatment option for malignant gliomas of less than 4 cm.

## **Benign intracranial neoplasms**

Benign neoplasms of the brain are slow-growing tumours that do not invade surrounding structures. Nevertheless, treatment to preserve neurological function can be challenging and complications serious. Approximately 30 to 40 per cent of all brain neoplasms are benign (Black 1995). The most common tumour types are meningiomas, acoustic neuromas and pituitary adenomas. Measuring the incidence of these tumours is difficult because benign neoplasms are not recorded in Australian cancer registries; therefore, the figures that follow are estimates only.

### **Meningiomas**

Meningiomas arise from the cells of the protective lining of the brain (meninges). They can progress from low-grade benign tumours to high-grade tumours that compress on the cortex of the brain or the cranial nerves. About 20 per cent of meningiomas are classified as clinically aggressive high-grade tumours (Black 1995; Lusa & Gutmann 2004).

Incidence is higher in women than men and presentation most commonly occurs in the seventh and sixth decade, respectively, although childhood cases also occur (Black 1995). Risk factors include exposure to ionising radiation, abnormalities of chromosome 22 and neurofibromatosis type II (Black 1995).

#### **Clinical need/burden of disease**

Meningiomas account for between 14 and 18 per cent of all intracranial neoplasms (Nakamura et al 2003). A population-based epidemiological study from the United States estimated an incidence of symptomatic disease in 2 per 100,000 population per year, with a higher figure when patients with incidental and autopsy diagnosis are included (Radhakrishnan et al 1995).

Patients may present with seizures, headaches and neurological deficits including of the cranial nerves, depending on the site of the tumour (Black 1995).

Between July 2003 and June 2004, 1,095 hospital separations were recorded in Australia with a principal diagnosis of benign meningioma (code D32, AIHW 2005a). Most of these patients (65%) were aged between 45 and 74 years. The average length of hospital stay was 10.3 days. Over the same period, 774 hospital procedures to remove tumours from cerebral meninges were performed in Australia (ICD-10-AM 39112-00; AIHW 2005b). The proportion of these admissions and procedures that were due to benign meningioma can not be determined.

#### **Standard treatment**

The primary treatment for meningiomas is surgery to remove the lesion or relieve symptoms. Total surgical resection may be possible depending on the location of the

tumour. Asymptomatic patients, in particular those over the age of 60 years, may also be observed with annual imaging tests. Post-surgical complications depend on tumour location and have been estimated at approximately 10 per cent, with mortality in up to 4 per cent of patients (Black 1995). Even after complete resection, recurrence occurs in up to 20 per cent of patients at 10 years, with higher rates for patients with residual tumour (Black 1995).

Radiotherapy is indicated for patients with inoperable, partially resected or recurrent tumours (Black 1995). SRS may offer advantages in these patients by allowing targeted therapy to limit radiation injury.

## **Acoustic neuroma**

Acoustic neuromas (vestibular schwannomas, acoustic neurinomas, nerve sheath tumours) arise from the Schwann cells lining the vestibular branch of the eighth cranial nerve (cochlear nerve). In some cases, they may erode the internal auditory canal and result in compression of the cranial nerves (Varlotto et al 1996).

Approximately 95 per cent of cases occur as a random isolated event (sporadic); 5 per cent are associated with the familial cancer syndrome called neurofibromatosis-2 (Black 1995). Sporadic cases are unilateral, with onset around 45-50 years of age, while neurofibromatosis-2 associated cases are typically bilateral, with onset at around 30 years of age (Glasscock, Hart, & Vrabec 1992). Neurofibromatosis-2 may have a different natural history from sporadic acoustic neuromas and respond differently to treatment and thus the distribution of neurofibromatosis-2 patients in reported studies may influence the overall results.

### **Clinical need/burden of disease**

Acoustic neuromas account for approximately 6 per cent of primary intracranial tumours, with an annual incidence of 0.3 to 1.3 per 100,000 individuals reported internationally (Lin et al 2005; Tos et al 2004). Based on these figures, up to 265 new cases of acoustic neuroma a year may be expected in Australia. Findings from a large MRI series in the United States estimated the prevalence of incidental acoustic neuromas at 2 per 10,000 individuals (Lin et al 2005).

Patients most commonly present with unilateral hearing loss due to compression or direct infiltration of the eighth cranial nerve. Other early symptoms are tinnitus and vestibular dysfunction including vertigo due to eighth nerve dysfunction. As the tumour progresses, hearing loss worsens and the vertigo is gradually replaced with disequilibrium. Symptoms due to trigeminal nerve and brainstem compression follow with mid-facial hypoesthesia and ataxia. If brain stem compression becomes severe, hydrocephalus may occur, resulting in visual loss and persistent headache (Table 2).

Acoustic neuromas occur with equal frequency in the left and right ear and are slightly more common in women than in men (Pollock et al 1998b; Tomasevic, Hook & Smee 1998). They are more common in patients aged between 40 and 59 years but may present at any age.

**Table 2 Symptomatic progression of acoustic neuroma with tumour growth**

Stage	Symptoms
Intracanalicular	Hearing loss Tinnitus Vertigo
Cisternal	Hearing loss worsens Vertigo diminishes Dysequilibrium increases
Brainstem compressive	Mid-facial and corneal hypoaesthesia (V cranial nerve) Occipital headache Ataxia begins
Hydrocephalic	Worsening trigeminal symptoms Gait deteriorates Headache becomes generalised Visual loss due to increased cranial pressure Lower cranial nerve dysfunction (hoarseness, dysphagia, aspiration etc) Long tract signs (hemiparesis)

Source: UCSF Acoustic Neuroma Team 1998.

Between July 2003 and June 2004, 388 hospital separations were recorded in Australia with a principal diagnosis of benign cranial nerve tumour (AIHW 2005a). Most of these patients were aged 45 years or older and the average length of hospital stay was 9.3 days. Over the same period, 286 hospital procedures for decompression of cranial nerves, including 49 cases for decompression of the facial nerve (ICD-10AM, 41569-00 49) and 237 cases for decompression of other cranial nerves (ICD-10-AM, 39112-00; AIHW 2005b). The proportion of those admissions and procedures that were due to acoustic neuroma and may be eligible for SRS can not be determined.

### Standard treatment

Recommended treatment is complete surgical resection (Sagar & Israel 2004). There are three standard surgical approaches (sub-occipital, translabyrinthine, and middle fossa). Each of these approaches has specific advantages and disadvantages and selection should be based on the training, experience and preference of the surgical team; the status of preoperative hearing; and the location and size of the lesion (NIH Consensus Development Panel 1991). Timely detection and treatment results in the preservation of hearing, with success rates of around 20 to 50 per cent for tumours of less than 2.5 cm (Black 1995). Treatment to preserve hearing is particularly critical for patients with neurofibromatosis-2 because of the likelihood of bilateral involvement.

Post-surgical complications occur in about 5 to 10 per cent of patients, with mortality rates of 2 to 4 per cent (Black 1995). Where complete resection is not possible due to the location of the lesion, or patient refusal, treatment alternatives include partial surgical removal, SRS and observation. Loss of hearing may also occur as a complication of treatment.

## Pituitary adenoma

Pituitary adenomas are a diverse group of tumours arising in the pituitary gland. They can be broadly classified as hormone secreting (70%) or non-hormone secreting (30%). Patients with hormone-secreting tumours present with clinical syndromes related to the type of hormone secreted. These include tumours that secrete prolactin (amenorrhoea-galactorrhea in women, impotence and infertility in men); growth hormone (acromegaly or gigantism); and adrenocorticotrophic hormone (Cushings's disease). Tumours that are non-hormone secreting cause symptoms such as visual loss or impaired pituitary function due to their mass effect (Sheehan et al 2005).

Incidence of pituitary adenoma is highest between the ages of 30 and 60 years and rare before the age of 20 years (Clayton 1999). The most common tumour types are prolactinoma and non-functioning tumours (Clayton 1999). There are no known risk factors, although they are associated with the familial cancer syndrome multiple endocrine neoplasia.

### Clinical need/burden of disease

Pituitary adenomas account for between 10 and 20 per cent of all primary brain tumours (Sheehan et al 2005). A population-based epidemiological study from the United States has estimated the incidence of symptomatic presentations at 2.4 per 100,000 population per year for (Radhakrishnan et al 1995). Based on these figures, approximately 490 new symptomatic cases of pituitary adenomas a year may be expected in Australia. This figure is higher for patients with subclinical disease. A systematic review and meta-analysis has estimated the prevalence of pituitary adenomas at 16.7 per cent based on radiological and autopsy findings (Ezzat et al 2004).

Between July 2003 and June 2004, 522 hospital separations were recorded in Australia with a principal diagnosis of pituitary adenoma (AIHW 2005a, D35.2). Most of these patients were aged between 40 years and 69 years of age and the average length of hospital stay was 7.0 days. Over the same period, 483 hospital procedures were performed involving total or partial removal of the pituitary gland (ICD-10-AM 39715-00, 39715-01, 90048-00, 90048-01, 90048-02; AIHW 2005b). The proportion of these admissions and procedures that may be eligible for SRS is not known.

### Standard treatment

Pituitary adenomas may be treated by observation, medication or surgery with or without radiotherapy. Appropriate treatment depends on the histological type and size of the tumour. When surgery is the treatment of choice, success rates for reduction of hormone levels in hormone-secreting tumours also vary according to the histological type.

Prolactinomas can usually be managed with medication. Surgery is reserved for patients who cannot tolerate medication, require urgent treatment due to rapid visual loss or wish to fall pregnant (Black 1995). Surgery for prolactinomas leads to a return to normal prolactin levels in 60 to 70 per cent of cases, with about 20 per cent recurrence after five years.

Surgical resection is the treatment of choice for growth hormone-secreting tumours and adrenocorticotrophic hormone-secreting tumours, with high success rates (Black 1995). Postoperative remission rates are 80 per cent or higher for growth hormone-secreting

tumours that are not large and do not invade surrounding structures (Black 1995). Surgery achieves cure rates of 90 per cent for Cushing's disease if the adrenocorticotropic hormone-secreting adenoma can be identified on preoperative imaging (Black 1995).

Postoperative complication rates of up to 10 per cent have been reported (Black 1995). These include cerebrospinal fluid leaks, impairment of other pituitary function and sinusitis, and 1 per cent of patients are at risk of visual loss.

Radiotherapy has a role in treating patients with inoperable, partially resected or recurrent tumours as well as those who refuse surgery (Black 1995). Complication rates range between 3 and 7 per cent and include visual loss due to radiation injury and second brain tumours (Black 1995). Around 50 per cent of patients go on to require medication due to impairment of pituitary function.

SRS may offer advantages by allowing targeted therapy to limit radiation injury. However, it may also carry an increased risk of visual damage due to the delivery of high doses of radiation close to the optic nerve (Black 1995).

## **Arteriovenous malformations**

Cerebral arteriovenous malformations (AVMs) are a complex tangle of abnormal cerebral arteries and veins linked by one or more fistulas. The fistulas allow high-flow, rapid arteriovenous shunting, which can induce arterial hypertension in vessels feeding the AVM and in neighbouring areas of the brain. Although it is still unclear what causes these abnormalities, it is thought that they may arise from developmental derangements at the embryonic stage of vessel formation, at the fetal stage or after birth (AVM Study Group 1999).

Cerebral AVMs vary considerably in size, location, vascular composition and clinical presentation. Accurate determination of the likely natural history and prognosis of an individual patient is difficult; they may grow, remain static, or spontaneously regress.

### **Disease classification**

AVMs are often graded to predict patient prognosis following treatment. The most common grading scale is the five-point Spetzler–Martin scale (Spetzler & Martin 1986). It is based on three parameters: AVM size, location and the type of venous drainage (Table 3). Scores between 1 and 3 are associated with lower risks of persistent neurological deficits following surgery (<3%) than those with higher scores (approximately 20%) (Hamilton & Spetzler 1994). This scale has also been used to predict prognosis in radiosurgical series, although it may not be directly applicable to this patient group. Some authors have also added a sixth category (VI) of 'inoperable'. One limitation is that patients with a Spetzler–Martin score of 3 are a heterogeneous group including up to four different lesion classifications (Lawton & UCSF Brain Arteriovenous Malformation Study Project 2003).

**Table 3 Spetzler–Martin Scale for evaluating prognosis after surgery**

Characteristic	No. points assigned
<i>Size</i>	
Small (maximum diameter <3cm)	1
Medium (maximum diameter 3–6cm)	2
Large (maximum diameter >6cm)	3
<i>Location</i>	
Noneloquent site	0
Sensorimotor, language, or visual cortex; hypothalamus or thalamus; internal capsule; brain stem; cerebellar peduncles; or cerebellar nuclei	1
<i>Pattern of venous drainage</i>	
Superficial only	0
Deep	1

More recently, Pollock and Flickinger (2002) developed a radiosurgery-based grading system for AVMs, derived from a multivariate analysis of variables predicting excellent outcome after Gamma Knife radiosurgery in a sample of 220 patients (see Table 4). ‘Excellent outcome’ was defined as complete nidus obliteration and no new development of neurological deficit. The score is derived by multiplying the AVM volume, the patient’s age and the AVM location by each variable’s coefficient, and summing the results. In testing the model in 136 AVM patients, all patients with a score of 1 or lower had excellent outcomes after Gamma Knife radiosurgery, compared with only 39 per cent of patients with AVM scores greater than 2.

**Table 4 Radiosurgery-based grading scale for evaluating prognosis<sup>1</sup>**

Characteristic	Coefficient
AVM volume (cm <sup>3</sup> )	0.1
Patient age (years)	0.02
AVM location <sup>b</sup>	0.3
Frontal or temporal = 0	
Parietal, occipital, intraventricular, corpus callosum, or cerebellar = 1	
Basal ganglia, thalamic, or brainstem = 2	

Abbreviation: AVM = arteriovenous malformation.

a. AVM score = (0.1)(AVM volume) + (0.02)(patient age) + (0.3)(AVM location).

b. When an AVM involves multiple sites, fractional values are used according to the number of sites (0.5 for two sites, 0.33 for three sites).

Source: Pollock and Flickinger 2002.

### Clinical need/burden of disease

Individuals with cerebral AVMs can present with a range of symptoms including intracranial haemorrhage, seizures, neurological deficits and intractable headache. In some cases the AVM may be asymptomatic and detected during investigations for other conditions.

A prospective evaluation of patients with untreated, symptomatic AVMs reported a 4 per cent annual bleeding rate, 1 per cent mortality rate and 1.7 per cent rate of severe morbidity. Over the 24-year follow-up period of this study, 34 per cent of AVM patients experienced haemorrhage, and of those, 85 per cent died or suffered severe morbidity (Ondra et al 1990; Wilkins 1985). A first haemorrhage has been reported to be associated

with a mortality of approximately 10 per cent, which increases to around 20 per cent for subsequent recurrent haemorrhages (Wilkins 1985). Other studies have indicated that the occurrence of a first haemorrhage is associated with an increased risk of subsequent haemorrhage (Pollock et al 1996; Brown & Wiebers 1988; Mast et al 1997). Seizures are the second most frequent presenting symptom after haemorrhage and may also be a clinical manifestation of minor haemorrhage. Ondra et al (1990) found that patients with AVM-related haemorrhage and patients with seizures had similar long-term morbidity and mortality.

Neurological deficits which are not associated with previous haemorrhage occur less frequently than seizures or bleeding and may be caused by several mechanisms, including decreased perfusion of normal brain tissue because of associated arterial stenoses, venous hypertension, or mass-effect caused by compression of brain parenchyma (Valavanis & Yasargil 1998). Headache which is not associated with acute cerebral haemorrhage is also a relatively frequent symptom experienced by patients with AVMs.

A population-based epidemiological study from the United States has estimated an annual detection rate of 1.34 per 100,000 population, of which approximately half may present with haemorrhage (Stapf et al 2003). Based on this figure, approximately 270 new cases of cerebral AVM may be expected to be detected in Australia each year.

Between July 2003 and June 2004, 318 hospital separations were recorded in Australia with a principal diagnosis of cerebral AVM (AIHW 2005a, Q28.2). Most patients were aged between 30 and 59 years (147/318, or 46%, of admissions); however, patient age was broadly distributed, with 117 admissions for patients less than 30 years, and 54 admissions for patients aged 60 years or older. The average length of hospital stay was 7.5 days. Over the same period, 181 hospital procedures were performed to excise an intracranial AVM (ICD-10-AM 39803-00; AIHW 2005b). The proportion of these admissions and procedures that may be eligible for SRS can not be determined.

### **Standard treatment**

The purpose of treatment is to obliterate the malformation in order to prevent haemorrhage. Treatment options include surgery, endovascular embolisation, radiosurgery and combinations of these treatments. There are no RCTs to guide appropriate treatment selection; however, the American Stroke Council has published practice recommendations based on the evidence available (Ogilvy et al 2001).

### **Surgery**

The primary advantages of surgical resection are the high cure rate and the immediate elimination of the risk of haemorrhage. The primary disadvantage is that it is an invasive treatment and therefore associated with the general risks of a craniotomy and anaesthesia, as well as the specific risks associated with the particular AVM, including haemorrhage, infection, cerebral oedema, stroke and death. The magnitude of these risks varies widely according to the Spetzler–Martin grade of the lesion (Ogilvy et al 2001; Choi & Mohr 2005). Case series have reported a favourable outcome in 92 to 100 per cent of patients with grade I lesions; this decreases to 57 per cent in patients with grade V lesions, with a long term mortality rate of 4.8 per cent (Ogilvy et al 2001).

### **Endovascular occlusion**

Endovascular occlusion (embolisation) involves the catheterisation of cerebral arteries for the local delivery of occlusive agents. Rates of complete AVM occlusion with embolisation alone have been disappointing, and thus it is generally used to decrease the size and bleeding risk of large lesions prior to surgery or radiosurgery or to occlude surgically inaccessible deep or dural feeding arteries. Palliative embolisation may be performed to reduce blood flow or venous hypertension in patients with progressive neurological symptoms or seizures due to large AVMs that are not amenable to surgery or radiosurgery (Ogilvy et al 2001). Complications include haemorrhage (2 to 4.7% of patients), neurological morbidity (2 to 5 %) and up to 1 per cent mortality (Ogilvy et al 2001).

### **Stereotactic radiosurgery**

Stereotactic radiosurgery involves the delivery of high-dose radiation to the AVM nidus to cause vascular injury and subsequent thrombosis with minimal injury to the surrounding brain tissue. The main advantage of radiosurgery is the avoidance of surgery and attendant risks, in particular for deeply located or otherwise inoperable AVMs and small AVMs in the eloquent cortex. The primary disadvantage is the long interval (two years or longer) from treatment to AVM obliteration, during which time the patient is not protected from haemorrhage (Ogilvy et al 2001; Choi & Mohr 2005). Other disadvantages include variable therapeutic effectiveness for different lesions, the risk of radiation necrosis and the need for long-term follow-up, including repeat angiography.

## **Existing procedures**

This section lists the theoretical advantages of existing procedures for the six indications described above.

### **Surgery**

- immediate removal of mass effect
- tissue biopsy for pathologic diagnosis (in particular, in patients with a diagnosis of cancer, approximately 10 per cent of cerebral lesions identified at imaging are not malignant)
- treatment of cancers that are unlikely to respond to radiotherapy (radiation-insensitive, large, and those that include haemorrhagic or cystic swellings)
- no risk of radiation necrosis
- may lead to better control of seizures than SRS due to removal of necrotic tissue.

### **Conventional radiotherapy**

- less invasive than surgery with decreased risk of haemorrhage and infection
- can treat large lesions
- outpatient treatment
- no anaesthetic risk.

## **Stereotactic radiosurgery**

- less invasive than surgery with decreased risk of haemorrhage and infection
- single treatment
- no anaesthetic risk
- less costly.

The underlying biological mechanism for Gamma Knife, Linac and CyberKnife radiosurgery is the same, and thus Gamma Knife shares the same theoretical advantages as Linac and CyberKnife. One difference is that the treatment area for Gamma Knife is restricted to spheres or combinations of spheres, whereas Linac can be delivered to other, more complex tumour shapes.

This report does not review the use of other technologies such as tomotherapy (Linac in a CT scanner with a microcollimator) that may be used to treat intracranial lesions.

## **Comparators**

Gamma Knife radiosurgery is assessed as a replacement or supplemental treatment to standard existing procedures for each of the six indications. The treatment comparisons for each indication are listed in the following section under the specific review question.

## **Marketing status of the technology**

The Gamma Knife unit was listed on the Australian Register of Therapeutic Goods on 14 April 1999 as AUST L 68655. As a listed, rather than a registered device, no evaluation of efficacy is required prior to listing.

## **Current reimbursement arrangement**

Gamma Knife radiosurgery is not specifically listed for reimbursement under the MBS (Australian Government Department of Health and Aged Care 2004). Linac radiosurgery is currently reimbursed under MBS Item Number 15600. This is a general listing for Stereotactic Radiosurgery that does not specify the type of technology used. It attracts a fee of \$1,473.30, which includes all radiation oncology consultations, planning, simulation, dosimetry and radiosurgery treatment.

## **Potential utilisation of Gamma Knife radiosurgery**

As described in the previous sections, it is not possible to estimate the size of the population eligible for Gamma Knife radiosurgery from existing data about cancer incidence and relevant Australian hospital diagnoses and procedures because only a subset of patients with the six conditions of interest will be eligible for SRS.

Furthermore, these data do not include the number of patients treated with conventional radiotherapy who may also be eligible for Gamma Knife radiosurgery.

Data about current utilisation of Linac to deliver SRS can be used to estimate the minimum number of patients eligible for Gamma Knife radiosurgery. There are currently six modified Linac facilities in Australia that can perform radiosurgery: NSW (2), Victoria (2), South Australia (1), WA (1), with none available in Tasmania or the Northern Territory (Advisory Panel 15 August 2005). A survey of the two public radiation oncology treatment centres in NSW reported that 97 patients were treated with single fraction Linac radiosurgery, and 76 patients were treated with fractionated radiosurgery with an average of 24 attendances per patient in 2004 (NSW Health 2005). This figure is likely to underestimate the true need for SRS services in the state based on recent evidence about the lack of adequate delivery of these services (Barton, Frommer, & sam Gabriel 2004).

# Approach to assessment

---

## The research questions

The review team worked with members of the advisory panel to develop specific questions addressing the use of Gamma Knife radiosurgery for the treatment of intracranial lesions. These questions were formulated *a priori* based on information about the disease area, current practice and the intended purpose of the technology.

Flow charts (see Appendix D) depicting the clinical pathways for treating each of the indications were developed with the advisory panel. These flow charts were used to define the potential role of Gamma Knife radiosurgery in treating intracranial lesions. The population, intervention, comparator and outcomes defined for the primary review questions are described in the following sections.

### Cerebral metastases

- population: patients with cerebral metastases
- intervention: Gamma Knife radiosurgery (alone or in combination with whole brain radiotherapy)
- comparators: surgery plus WBRT, or observation
- outcomes: survival, quality of life, steroid dependence.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of Gamma Knife radiosurgery (alone or in combination with whole brain radiotherapy) for treating cerebral metastases compared with surgery plus whole brain radiotherapy, or observation?

### Arteriovenous malformations

- population: patients with arteriovenous malformations (AVMs)
- intervention: Gamma Knife radiosurgery
- comparators: Linac radiosurgery, CyberKnife radiosurgery, surgery, or observation
- outcomes: obliteration, necrosis, morbidity/mortality (surgical and non-surgical), bleeding, death from haemorrhage.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of Gamma Knife radiosurgery for treating arteriovenous malformations (AVMs) compared with Linac radiosurgery, CyberKnife radiosurgery, surgery, or observation?

## Acoustic neuromas

- population: patients with acoustic neuromas
- intervention: Gamma Knife radiosurgery
- comparators: Linac radiosurgery, CyberKnife radiosurgery, surgery, or no treatment
- outcomes: progression, hearing, facial palsy, mortality, quality of life, survival, secondary malignancy.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost effectiveness of Gamma Knife radiosurgery for treating acoustic neuromas compared with Linac radiosurgery, CyberKnife radiosurgery, surgery, or no treatment?

## Primary malignant lesions

- population: patients with primary malignant lesions
- intervention: Gamma Knife radiosurgery boost (in combination with surgery and external beam radiotherapy)
- comparators: Linac boost (in combination with surgery and external beam radiotherapy), CyberKnife boost (in combination with surgery and external beam radiotherapy), surgery plus radiotherapy, or no treatment
- outcomes: quality of life, survival.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of Gamma Knife radiosurgery boost (in combination with surgery and external beam radiotherapy) for treating primary malignant lesions compared with Linac or CyberKnife boost (in combination with surgery and external beam radiotherapy), surgery plus radiotherapy, or no treatment?

## Meningiomas

- population: patients with meningiomas
- intervention: Gamma Knife radiosurgery (alone or in combination with surgery)
- comparators: Linac radiosurgery (alone or in combination with surgery), CyberKnife radiosurgery (alone or in combination with surgery), surgery, radiotherapy (alone or in combination with surgery), or observation
- outcomes: progression, radiation necrosis, surgical morbidity/mortality, neurological damage.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of Gamma Knife radiosurgery (alone or in combination with surgery) for treating meningiomas compared with Linac radiosurgery (alone or in combination with surgery), CyberKnife radiosurgery (alone or in combination with surgery), surgery, radiotherapy (alone or in combination with surgery), or observation?

### **Pituitary adenomas**

- population: patients with pituitary adenomas
- intervention: Gamma Knife radiosurgery (alone or in combination with surgery)
- comparators: Linac radiosurgery (alone or in combination with surgery), CyberKnife radiosurgery (alone or in combination with surgery), surgery, radiotherapy (alone or in combination with surgery), or observation
- outcomes: hormone function, visual defects, progression, temporal lobe necrosis (radiotherapy), surgical morbidity/mortality, cognitive function.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of Gamma Knife radiosurgery (alone or in combination with surgery) for treating pituitary adenomas compared with Linac radiosurgery (alone or in combination with surgery), CyberKnife radiosurgery (alone or in combination with surgery), surgery, radiotherapy (alone or in combination with surgery), or observation?

### **Review of literature**

The MSAC's recommendations are based primarily on the findings of a systematic literature review conducted by the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The medical literature was searched to identify relevant primary studies and systematic reviews for the period between 2001 and September 2005. Searches were conducted via electronic databases as listed in Table 5. The search was limited by publication date in order to update MSAC's previous assessment of Gamma Knife radiosurgery, published in 2000, and a health technology assessment report conducted by the Alberta Heritage Foundation for Medical Research, Canada (Hailey 2002). Furthermore, compared with the previous MSAC review, the scope of the assessment was narrowed to include only comparative studies of Gamma Knife radiosurgery and alternative treatments.

**Table 5 Electronic databases searched in this review**

Database	Period covered
Medline	2001–September 2005
EMBASE	2001– September 2005
Pre-Medline	2001– September 2005
Current Contents	2001– September 2005
CINAHL	2001– September 2005
All-EBM databases	– September 2005
—ACP Journal Club (ACP)	
—Cochrane Database of Systematic Reviews (COCH)	
—Database of Abstracts of Reviews of Effectiveness (DARE)	
—Cochrane Controlled Trials Register	

### Search strategy

The search strategy was developed using the key elements of the clinical questions. It contained search terms for both Gamma Knife and stereotactic radiosurgery and combined these with search terms specific to each of the six indications. The appropriateness of the terms and logic of the search strategy was reviewed by a specialist in electronic database searching.

The search strategy shown in Table 6 was used to identify papers in Medline. A similar search strategy using the same search terms was also employed for the EMBASE, Pre-Medline, Current Contents, CINAHL and the All-EBM databases.

**Table 6 Search strategy**

Number	Search terms
1	exp radiosurgery/ or radiosurg\$.mp.
2	exp stereotaxic techniques/ or stereotactic.mp.
3	Gamma Knife.mp.
4	or/1-3
5	exp intracranial arteriovenous malformations/
6	((arteriovenous malformation\$ or AVM\$) adj3 (brain or cerebral or intracranial)).mp.
7	or/5-6
8	exp brain neoplasms/
9	(metasta\$ adj3 (brain or cerebral or intracranial)).mp.
10	((lesion\$ or neoplasm\$ or tumor\$ or cancer\$ or carcinoma\$) adj3 (brain or cerebral or intracranial)).mp.
11	exp glioma/ or (glioma\$ or glioblastoma\$).mp.
12	or/8-11
13	exp neuroma, acoustic/ or (acoustic neuroma\$ or vestibular schwannoma\$).mp.
14	exp pituitary neoplasm/ or pituitary adenoma\$.mp.
15	exp meningioma/ or meningioma\$.mp.
16	7 or 12 or 13 or 14 or 15
17	4 and 16
18	animals/
19	humans/
20	18 not (18 and 19)
21	17 not 20
22	case report.ti,ab. or case reports.pt.
23	letter.pt.
24	historical article.pt.
25	review of reported cases.pt.
26	review multicase.pt.
27	or/22-26
28	21 not 27
29	limit 28 to yr = "2001-2005"

Reference lists of publications were also searched for additional relevant citations that may have been inadvertently missed in searches of major databases.

In addition to the databases already listed, the websites of international health technology assessment (HTA) agencies listed in Table 7 were searched.

**Table 7 Health technology assessment sites searched**

Organisation	Website
International Network of Agencies for Health Technology Assessment (INAHTA)	<a href="http://www.inahta.org">www.inahta.org</a>
British Columbia Office of Health Technology Assessment (Canada)	<a href="http://www.chspr.ubc.edu.ca/bcohta">www.chspr.ubc.edu.ca/bcohta</a>
Swedish Council on Technology Assessment in Healthcare (Sweden)	<a href="http://www.sbu.se">www.sbu.se</a>
Oregon Health Resources Commission (USA)	<a href="http://www.ohpr.state.or.us/ohrc">www.ohpr.state.or.us/ohrc</a>
Minnesota Department of Health (USA)	<a href="http://www.health.state.mn.us">www.health.state.mn.us</a>
Canadian Coordinating Office for Health Technology Assessment (Canada)	<a href="http://www.ccohta.ca">www.ccohta.ca</a>
Alberta Heritage Foundation for Medical Research (Canada)	<a href="http://www.ahfmr.ca">www.ahfmr.ca</a>
Veteran's Affairs Research and Development Technology Assessment Program (USA)	<a href="http://www.va.gov/resdev">www.va.gov/resdev</a>
National Library of Medicine Health Service/Technology Assessment text (USA)	<a href="http://text.nlm.nih.gov">http://text.nlm.nih.gov</a>
NHS Health Technology Assessment (UK)	<a href="http://www.hta.nhsweb.nhs.uk">www.hta.nhsweb.nhs.uk</a>
Office of Health Technology Assessment Archive (USA)	<a href="http://www.wws.princeton.edu/~ota">www.wws.princeton.edu/~ota</a>
Institute for Clinical Evaluative Science (Canada)	<a href="http://www.ices.on.ca">www.ices.on.ca</a>
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	<a href="http://www.cets.gouv.qc.ca">www.cets.gouv.qc.ca</a>
National Information Centre of Health Services Research and Health Care Technology (USA)	<a href="http://www.nlm.nih.gov/nichsr/nichsr.html">http://www.nlm.nih.gov/nichsr/nichsr.html</a>
Finnish Office for Health Technology Assessment (Finland)	<a href="http://www.stakes.fi/finoha/linkit/">http://www.stakes.fi/finoha/linkit/</a>
Institute Medical Technology Assessment (Netherlands)	<a href="http://www.bmg.eur.nl/imta/">http://www.bmg.eur.nl/imta/</a>
AETS (Spain)	<a href="http://www.isciii.es/unidad/aet/cdoc.htm">http://www.isciii.es/unidad/aet/cdoc.htm</a>
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	<a href="http://www.anaes.fr">www.anaes.fr</a>

### Eligibility criteria for studies

The search strategy retrieved a total of 2,718 non-duplicate citations. The citations were screened by one reviewer to determine eligibility using the criteria outlined in Table 8. A representative sample of 500 citations (18%) was independently assessed by a second reviewer. Agreement between reviewers was 0.82 (kappa statistic). All potentially eligible articles identified using this screening process were retrieved and both reviewers independently assessed all retrieved articles for eligibility and quality. Discrepancies in the results of this eligibility assessment were resolved by discussion.

**Table 8 Study exclusion criteria**

<b>1. Not a clinical study</b>
Clinical studies included. Non-systematic reviews, case reports, case series, comparative studies of less than 20 patients (or with less than 10 patients in the treatment or comparator arms), letters, editorials, animal, in-vitro and laboratory studies excluded. Studies comparing series with unrelated historical controls excluded.
<b>2. Wrong patient group</b>
Studies were to include patients with arteriovenous malformations (AVMs), cerebral metastases, primary malignant brain lesions, acoustic neuromas, pituitary adenomas, or meningiomas.
<b>3. Wrong intervention</b>
Studies were to use Gamma Knife radiosurgery. Studies will not be excluded if $\geq 75$ per cent of the sample receives Gamma Knife radiosurgery and the remainder receives Linac radiosurgery.
<b>4. Wrong comparator</b>
Studies were to use surgery, Linac radiosurgery, radiotherapy, CyberKnife radiosurgery, or combinations thereof, as comparators.
<b>5. Wrong outcomes</b>
Outcomes vary by indication, but include hormone function, visual defects, progression, temporal lobe necrosis (radiotherapy), surgical/non-surgical morbidity/mortality, cognitive function, neurological damage, obliteration, necrosis, bleeding, death from haemorrhage, hearing, facial palsy, quality of life, survival, secondary malignancy.
<b>6. Not in English</b>
Only studies available in English were eligible for inclusion.

Based on these criteria, 2,699 papers (99%) were excluded from this review.

Four health technology reports, one practice guideline and four published systematic reviews were identified in the search and fulfilled the inclusion criteria for the review. The HTA reports were published by the Alberta Heritage Foundation for Medical Research (Hailey 2002), the Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario (MAS 2002), the Agence d'évaluation des technologies et des modes d'intervention en sante (AETMIS 2004), and the Wessex Institute for Health Research and Development (Mitchell 2001). The practice guideline was published by the Program in Evidence-Based Care (Laperriere, Perry & Zuraw 2004). Two RCTs were found. Eight comparative, non-randomised cohort studies that met the inclusion criteria were identified for those indications where RCT evidence was not available.

The QUORUM flowchart (Figure 1) summarises the results of the literature search and the application of the study exclusion criteria.

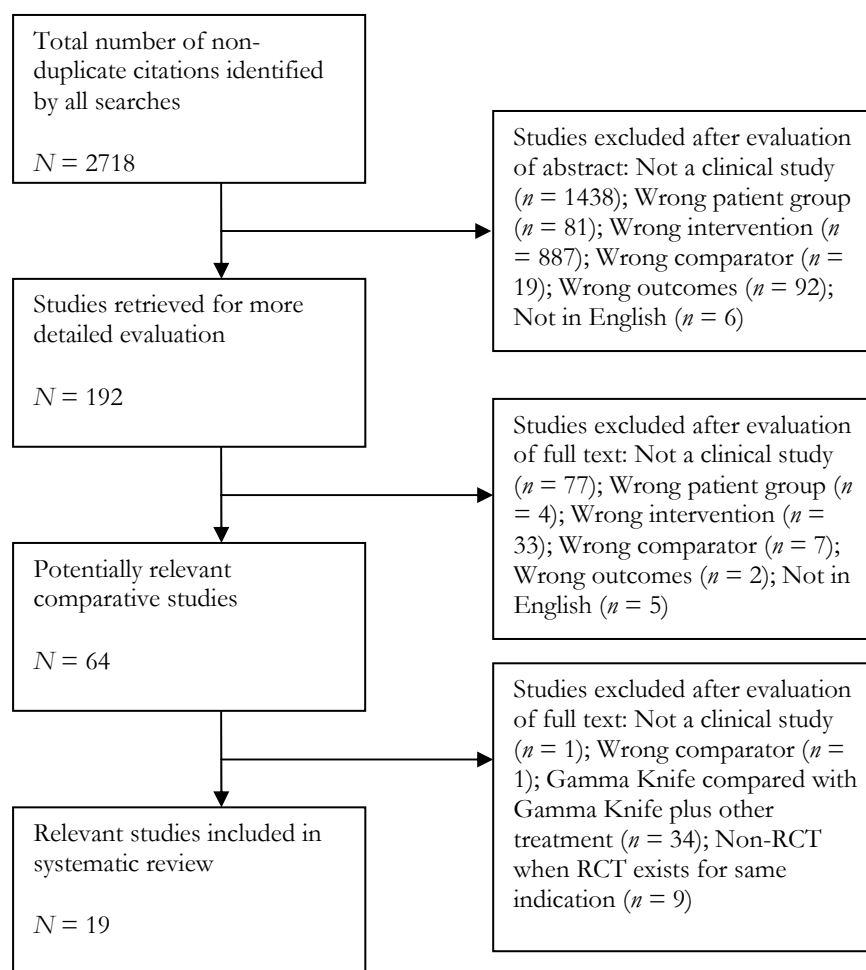


Figure 1 QUORUM flowchart of study inclusions and exclusions

## Appraisal

### Assessment of eligible studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (Bertalanffy et al 2001). These dimensions (Table 9) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

**Table 9 Evidence dimensions**

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design. <sup>a</sup>
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

<sup>a</sup> See Table 10.

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 10.

**Table 10 Designations of levels of evidence<sup>a</sup>**

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant RCTs
II	Evidence obtained from at least one properly-designed RCT
III-1	Evidence obtained from well-designed pseudo RCTs (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Abbreviation: RCT = randomised controlled trial.

<sup>a</sup> Modified from NHMRC 1999.

## Quality appraisal tools

Study quality refers to the extent to which the methods used within the chosen study design are adequate to avoid potential bias. A structured appraisal to assess the quality of all included studies was performed. A standard checklist for quality appraisal of RCTs is presented in Table 11, and the checklist applied for non-randomised controlled studies is given in Table 12.

## Data extraction

Data were extracted using a standardised instrument designed for this review. Data extraction was performed by one reviewer and checked by a second reviewer, with any discrepancies resolved by discussion. The data extraction tables are provided in Appendix C.

**Table 11 Checklist for appraising the quality of randomised controlled studies of interventions<sup>a</sup>**

<p>1. Method of treatment assignment</p> <ul style="list-style-type: none"> <li>a. Correct, blinded randomisation method described OR randomised, double-blind method stated AND group similarity documented</li> <li>b. Blinding and randomisation stated but method not described OR suspect technique (eg allocation by drawing from an envelope)</li> <li>c. Randomisation claimed but not described and investigator not blinded</li> <li>d. Randomisation not mentioned</li> </ul> <p>2. Control of selection bias after treatment assignment</p> <ul style="list-style-type: none"> <li>a. Intention to treat analysis AND full follow-up</li> <li>b. Intention to treat analysis AND &lt;15 per cent loss to follow-up</li> <li>c. Analysis by treatment received only OR no mention of withdrawals</li> <li>d. Analysis by treatment received AND no mention of withdrawals OR more than 15 per cent withdrawals/loss-to-follow-up/post-randomisation exclusions</li> </ul> <p>3. Blinding</p> <ul style="list-style-type: none"> <li>a. Blinding of outcome assessor AND patient and care giver</li> <li>b. Blinding of outcome assessor OR patient and care giver</li> <li>c. Blinding not done</li> </ul> <p>4. Outcome assessment (if blinding was not possible)</p> <ul style="list-style-type: none"> <li>a. All patients had standardised assessment</li> <li>b. No standardised assessment OR not mentioned</li> </ul>
---

<sup>a</sup> NHMRC 2001, modified from I. Chalmers, *Cochrane Handbook*.

**Table 12 Checklist for appraising the quality of non-randomised studies of interventions<sup>a</sup>**

<ol style="list-style-type: none"> <li>1. Were subjects selected prospectively or retrospectively?</li> <li>2. Was the intervention reliably ascertained?</li> <li>3. Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?</li> <li>4. Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors?</li> <li>5. Did the study adequately control for potential confounding factors in the design or analysis?</li> <li>6. Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?</li> <li>7. Was follow-up long enough for outcomes to occur?</li> <li>8. What proportion of the cohort was followed-up and were there exclusions from the analysis?</li> <li>9. Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?</li> </ol>
--

<sup>a</sup> Adapted from Khan, ter Riet, Popay et al 2001.

## Expert advice

An advisory panel with expertise in neurology, neurosurgery, radiation oncology and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

# Results of assessment

---

Results of the assessment for each indication are presented separately on the following pages. Each review incorporates an assessment of the safety and the effectiveness of Gamma Knife radiosurgery. An overall assessment of economic considerations is presented after the six reviews.

## Cerebral Metastases

### Is it safe?

#### Previous MSAC assessment

MSAC's previous assessment of safety considered one RCT, and event rates from one retrospective cohort study and 14 SRS case series. It was found that complications were generally poorly reported. Acute complications included radiation-induced oedema in approximately 20 per cent of patients, and nausea, vomiting, seizures and increased paresis in up to 10 per cent of patients. Radiation necrosis (either suspected or confirmed) developed as a significant long-term complication in up to 10 per cent of patients, with 6 per cent requiring treatment, and fatal radiation necrosis occurring in 1 per cent. Comparisons between treatments were not considered to be appropriate based on the evidence available.

#### Systematic reviews, HTAs and practice guidelines

Previous systematic reviews have addressed the safety of Gamma Knife radiosurgery to varying degrees. Tsao et al (2005a) and Mehta et al (2005) quote the rates of toxicity from an RCT by Andrews et al (2004), and conclude that there is a non-statistically significant increased risk of toxicity in SRS boost to WBRT compared with WBRT alone. Rates of acute grades 3 and 4 toxicity were 3 per cent, and late grades 3 and 4 toxicity were 6 per cent. (The trial reported by Andrews et al is discussed further later). Another HTA quoted case series evidence in which 22 per cent of patients experienced severe neurotoxicity (MAS 2002). In 42 per cent of patients experiencing severe neurotoxicity this was irreversible. In 3 per cent of all patients neurotoxicity was fatal.

Two further reviews simply describe Gamma Knife as being safe (AETMIS 2004) or as having few associated complications (Mitchell 2001).

#### Primary studies

The literature search identified one RCT investigating the safety of SRS (by Gamma Knife or Linac) in patients with up to three cerebral metastases (Andrews et al 2004). The trial considered SRS as a boost to WBRT ( $n = 164$ ) compared with WBRT alone ( $n = 167$ ). Acute (within 90 days of treatment) and late (90 days or more after treatment) radiation-related toxicities were recorded according to the grading scheme developed by the Radiation Therapy Oncology Group (RTOG 2005). The RTOG grading scheme classifies toxicities on a five-point scale ranging from 0 to 4. Zero indicates an absence of symptoms, while grade 1 relates to mild, grade 2 to moderate, grade 3 to severe, and grade 4 to life-threatening toxicities. Mean follow-up for late toxicities is not reported.

The rate of acute toxicities reported in the SRS plus WBRT group (63%) did not differ significantly from the rate reported in the WBRT alone group (61%) ( $p = 0.75$ ). The most common toxicity reported in both groups was acute skin symptoms, with 46 per cent of patients in both groups reporting such toxicities. These were primarily grade 1 in both groups (scattered macular or papular eruption or erythema that is asymptomatic). Nausea/vomiting was the next most common symptom, reported in 17 and 15 per cent of SRS plus WBRT and WBRT alone patients, respectively. Again, these were primarily grade 1 toxicities (defined for nausea as being able to eat with reasonable intake, and one episode in 24 hours for vomiting). However, there were five grade 3 or 4 toxicities in three patients in the SRS group, compared with none reported in patients treated by WBRT alone. Four of these acute toxicities in the SRS group were neurological, with three being central (one of these was grade 4), and one being peripheral. Four patients in this analysis were lost to follow-up in the SRS group, and one was lost in the WBRT alone group.

In terms of late toxicity, the rates reported by both groups were again similar. For those undergoing SRS plus WBRT, late toxicities were reported in 26 per cent of patients, compared with 24 per cent treated with WBRT alone ( $p = 0.79$ ). However, the symptom profile appeared to differ between the groups. The most common toxicity in SRS plus WBRT patients was central neurological symptoms (14%), while the most common toxicity among those treated with WBRT alone was chronic skin symptoms (13%). There were inconsistencies in the reporting of grades 3 and 4 toxicities in the SRS group, but there seemed to be six patients with such toxicities (six toxicities total), compared with three patients (four toxicities total) treated with WBRT alone. Grades 3 or 4 toxicities in SRS plus WBRT included nausea/vomiting, hearing loss, central neurological and 'other' toxicities. For WBRT alone, grades 3 or 4 toxicities included nausea/vomiting, hearing loss, and central neurological symptoms. There was substantial loss to follow-up in both treatment groups, with 31 per cent of SRS plus WBRT patients and 33 per cent of WBRT alone patients being excluded from the assessment of late toxicities. These losses are not explained, but are most likely due to patient deaths.

## Discussion

Based on the results reported by Andrews et al (2004), it can be noted that the addition of SRS to WBRT results in similar rates of acute and late radiation-related complications to WBRT alone. However, both acute and late complications appeared to be more severe with the addition of SRS, with a slightly increase risk of RTOG grades 3 or 4 toxicities. This interpretation is consistent with previous systematic reviews (Mehta et al 2005; Tsao et al 2005a). However, it should be considered that SRS was delivered by both Gamma Knife and Linac in this trial, and the number of Gamma Knife patients specifically cannot be determined. Hence, the degree to which this finding applies to Gamma Knife is unclear. Additionally, this study was not powered to detect differences between treatments in terms of safety outcomes, and therefore it is possible that more pronounced differences between treatments could become evident with larger sample sizes. Comparisons between Gamma Knife and Linac radiosurgery in terms of safety were not addressed by this study. No studies were identified which compared Gamma Knife with CyberKnife radiosurgery for the treatment of cerebral metastases.

Case series studies were not reviewed due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret. The previous MSAC assessment identified such difficulties in its review of case series evidence for the safety of Gamma Knife

radiosurgery, and comparative conclusions were unable to be drawn due to these problems.

## **Conclusions**

There is Level II evidence which suggests that the addition of SRS to WBRT results in a slightly increased risk of serious radiation-related toxicity compared with WBRT alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. The present review is unable to update the conclusions of the previous MSAC assessment in terms of the relative safety of Gamma Knife and Linac radiosurgery, and there were no studies on which to base conclusions regarding the comparative safety of Gamma Knife and CyberKnife radiosurgery. The comparative safety of these different types of SRS remains uncertain. Similarly, no conclusions are possible regarding the comparative safety of Gamma Knife radiosurgery and surgery plus WBRT.

## **Is it effective?**

### **Previous MSAC assessment**

The previous MSAC assessment considered a single RCT comparing SRS plus WBRT versus WBRT alone (Kondziolka et al 1999). This study demonstrated improved local control in the radiosurgery arm, but no difference in survival between the two treatments. However, the trial was small and problematic in terms of the method of randomisation and its general susceptibility to bias, and was considered likely to overestimate the efficacy of radiosurgery. Further, although uncontrolled studies supported these findings, substantial heterogeneity among case series studies was identified. Hence, it was concluded that no definitive conclusions regarding comparative survival between SRS plus WBRT versus WBRT alone could be made (MSAC 2001). Additionally, it was noted that there was insufficient information to compare Gamma Knife with Linac radiosurgery.

### **Systematic reviews, HTAs and practice guidelines**

Six systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for cerebral metastases. None of the reviews attempted a statistical synthesis of effectiveness data in the form of a meta-analysis due to varying characteristics of the primary studies. Three reviews included evidence from RCTs, and two provided summaries of cohort or case series studies alone. Each of the reviews included studies considered either in the previous MSAC review or in the present one. One such review (MAS 2002) updated the previous MSAC assessment of Gamma Knife radiosurgery by extending the search period by two years. Two reviews provided sufficient information to meet all the specified criteria for high quality reviews (Mehta et al 2005; Tsao et al 2005a).

Only one review sought to specifically address the effectiveness of Gamma Knife radiosurgery (MAS 2002). Each of the other reviews, to varying degrees, reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery. Table 13 describes the populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

**Table 13 Cerebral metastases: populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	43 studies: 1 RCT 5 cohorts 34 case series	Cerebral metastases	GK or Linac Alone or in combination with surgery or WBRT	Not defined <i>a priori</i> . Studies compared GK with Linac, WBRT, surgery, and surgery plus WBRT.	Not defined <i>a priori</i> . Studies considered local control and survival.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
Tsao et al 2005a	3 RCTs	Adult patients with single or multiple brain metastases from cancer of any histology	GK or Linac In combination with WBRT	WBRT	Survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, toxicity.	High quality.
Mehta et al 2005	10 studies: 3 RCTs 7 cohort or case series	Adult patients with single or multiple brain metastases from cancer of any histology	GK or Linac (single fraction) In combination with WBRT	WBRT	Tumour control or response, survival, quality of life or symptom control, toxicity	High quality.
AETMIS 2004	12 case series	Cerebral metastases	GK or Linac	Not defined <i>a priori</i> . Comparisons made between GK and Linac.	Not defined <i>a priori</i> . Considered safety, effectiveness and quality of life.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
MAS 2002	4 studies: 1 RCT 1 cohort 2 case series	Cerebral metastases	GK With or without WBRT	Not defined <i>a priori</i> . Comparisons made between GK, Linac, and WBRT.	Not defined <i>a priori</i> . Considered safety, and tumour control.	Specific inclusion criteria per indication not provided. Literature search was limited. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
Mitchell 2001	3 studies: 1 systematic review 2 cohorts	Cerebral metastases	SRS	Not defined <i>a priori</i> . Comparisons made between GK, Linac, and WBRT.	Safety and efficacy. Considered safety, tumour control, functional effects and quality of life.	Specific inclusion criteria per indication not provided. Literature search was not described.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en santé; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; MAS = Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario; RCT = randomised controlled trial; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

## **Hailey 2002**

This systematic review, published by the Alberta Heritage Foundation for Medical Research in Canada, addressed multiple indications for Gamma Knife radiosurgery (including cerebral metastases), and along with the previous MSAC assessment, provides the basis for the present update review. The review was generally of good quality, but although general inclusion criteria are described, criteria specific to each indication were not stated. A single reviewer applied the inclusion criteria and extracted data, and hence there were no validity checks on these methods. Additionally, the method of quality assessment of included studies was not described.

The search identified one RCT comparing Gamma Knife radiosurgery plus WBRT to WBRT alone, which was also considered in the previous MSAC assessment (Kondziolka et al 1999). In addition, two cohort studies comparing Gamma Knife and Linac radiosurgery were included, along with one cohort study comparing Gamma Knife radiosurgery plus surgery with surgery plus WBRT, and two case control studies comparing Gamma Knife radiosurgery with surgery (one of these, [Muacevic et al 1999] was included in MSAC's previous assessment). These studies were supplemented by case series examining Gamma Knife and Linac radiosurgery individually, many of which were also included in the previous MSAC report.

Comparisons between Gamma Knife radiosurgery and WBRT versus WBRT alone were based primarily on the RCT which indicated that SRS in addition to WBRT was superior to WBRT alone in terms of time to local treatment failure. The authors noted that this finding was corroborated by some of the other comparative studies included in the review. Furthermore, in comparing Gamma Knife and Linac radiosurgery, one cohort study found no difference in the rates of local or distant brain relapse between these treatments. No conclusive comparison between Gamma Knife radiosurgery and surgery was possible given selection issues, small patient numbers and methodological issues inherent in the included studies.

## **Tsao et al 2005a**

This high quality review assessed radiotherapeutic management of single or multiple brain metastases from cancer of any histology in adult patients. Stereotactic radiosurgery was one modality that was evaluated, with the comparison of interest being SRS plus WBRT versus WBRT alone. The review included three RCTs. Two of the trials used Gamma Knife radiosurgery in the SRS study arm; one of them was considered in the previous MSAC evaluation (Kondziolka et al 1999), and the other was reported in abstract form only. The third included trial used either Gamma Knife or Linac radiosurgery to deliver SRS. This study is also included in the present assessment and is described in further detail below (Andrews et al 2004). All of these studies included patients with multiple brain metastases.

The authors noted that these studies show no overall benefit of the addition of SRS to WBRT over WBRT alone in terms of survival for patients with multiple brain metastases. Patients undergoing radiosurgery boost have been shown to have better one-year local brain control; however, a large RCT has shown no difference between the treatments in time to intracranial tumour progression. In light of these findings, it was concluded that the addition of SRS to WBRT for patients with 2 to 4 brain metastases remains controversial.

### **Mehta et al 2005**

This high-quality systematic review was undertaken on behalf of the American Society for Therapeutic Radiology and Oncology (ASTRO). The same trials considered by Tsao et al (2005a) were considered; however, these were also supplemented by seven retrospective cohort and case series studies including more than 100 patients (none of which were included in the previous MSAC assessment). The review questions considered the efficacy of SRS with or without WBRT compared with WBRT alone in adult patients with single or multiple brain metastases of any histology. However, most studies examining SRS alone compared this treatment with SRS plus WBRT (ie, radiosurgery was used in both arms), and hence these results are not presented here.

In terms of survival, it was noted that one high-quality RCT demonstrated significantly improved survival in a selected subgroup of patients with single metastases who received SRS as a boost to WBRT, compared with similar patients who received WBRT alone. However, RCTs had demonstrated that overall survival was not improved by radiosurgery boost compared to WBRT alone in patients with multiple metastases.

The review noted that all three RCTs found that patients receiving SRS plus WBRT had significantly improved rates of local brain control than those receiving WBRT only. Patients included in these studies had up to four metastases. Further, one trial also reported a significant improvement in Karnofsky Performance Score and statistically greater ability to taper down on steroid use in the SRS arm. Quality of life was not addressed by a validated instrument in any of the included studies.

### **AETMIS 2004**

This systematic review, although published in English in 2004, was conducted in 2002 and was first published in French in the same year. Multiple indications are addressed, including cerebral metastases. Quality assessment of included studies is not described in this report. Inclusion criteria applied to primary studies, and the methods used to apply these criteria and extract data are not stated.

Twelve case series, six each considering Gamma Knife and Linac radiosurgery, were included in the review. Two of these were also included in the previous MSAC assessment. It is possible that some of the studies were cohort studies comparing SRS with other treatments; however, no comparisons were described. The author notes that the primary studies were heterogeneous and of low methodological quality. However, it is concluded that SRS seems to be effective in certain carefully selected cases, with the main advantage of SRS over conventional radiotherapy being improvement in the patient's quality of life. However, the conclusions from this report appear to be based, at least in part, on studies that were not included in the systematic review itself.

### **MAS 2002**

This 'rapid response HTA' updated the previous MSAC assessment of Gamma Knife radiosurgery by extending the search until April 2002. However, the search strategy was not extensive, and it is possible that studies may have been missed. In addition, no inclusion criteria for primary studies were presented, the application of methods for the review was not described, and there was no discussion of the quality of the included studies.

In addressing cerebral metastases, the review identified one preliminary abstract report comparing SRS plus WBRT with WBRT alone (the full publication of this trial [Andrews

et al 2004] is included in the present MSAC assessment and is discussed later). In addition, one cohort study comparing Gamma Knife and Linac radiosurgery was included, along with two case series using Gamma Knife radiosurgery. The conclusions were based on single studies. On the basis of the RCT, it was concluded that there was no benefit of SRS over WBRT when employed as a first line radiation treatment. However, based on the cohort study, it was also concluded that SRS is beneficial in treating recurrent metastases following front-line radiation therapy, and that Gamma Knife improved local control compared with Linac.

### **Mitchell 2001**

This brief review considered SRS compared with 'conventional techniques' for patients with cerebral metastases (among other indications), and updated a previous review published in 1998. The quality of the review cannot be assessed adequately, as information about inclusion criteria, the search strategy, application of methods, and detailed data from the included studies are not presented.

On the basis of one systematic review and two cohort studies (one of which was considered in the previous MSAC review), it was concluded that SRS may have similar functional effects compared with conventional techniques, but that this conclusion must be regarded as tentative in the absence of controlled studies. Further, it was found that SRS may provide good local control and improved quality of life, with low morbidity and few complications; however, these conclusions were tentative given the poor methodological quality of the included studies.

### **Primary study: Andrews et al 2004**

One RCT was identified as being published since the previous MSAC assessment and the HTA report by Hailey (2002). This multicentre trial compared SRS (by either Gamma Knife or Linac) in addition to WBRT with WBRT alone in patients with up to three brain metastases. The primary outcome was survival, and secondary outcomes included tumour response and control rates, overall intracranial recurrence rates, cause of death and performance measurements.

This trial was considered to be of high quality based on the NHMRC checklist for appraising the quality of studies of interventions (NHMRC 2000). Patients were stratified by the number of metastases (one versus two or three) and the presence or absence of extracranial disease. Randomisation was carried out by computerised techniques at a single centre, and was conducted by permuted blocks within strata. Sample size calculations were based on a power of 80 per cent to detect an improvement in the primary outcome of median survival time from 7.1 to 10.6 months after treatment. Further, sample size calculations were made to detect a 75 per cent improvement in median survival time in single metastasis patients with 80 per cent power. A target sample size of 326 patients was derived.

The statistical methodology is well described. Since the single metastasis subgroup was accounted for in sample size calculations, adjustment was not made for multiple comparisons for this subgroup. An adjusted significance level of 0.0056 was applied to nine other subgroup survival analyses. However, adjusted significance levels for multiple comparisons were not applied to the analysis of performance measures (KPS, steroid use, Mini-Mental Status Examination (MMSE)). Analysis was by intention to treat.

The primary outcome measure for this trial was survival. Cause of death was either ascribed to be neurological or systemic, with neurological death occurring when the patient had stable systemic disease but succumbed to intracranial disease progression which was associated with progressive neurological dysfunction. Tumour control, progression and recurrence were measured by clinical and MRI examinations at participating institutions at three-month intervals up to one year after treatment. Central review of MRI scans occurred at three months and one year. Local control was defined as unchanged or improved serial post-treatment MRI scans. Progressive disease was defined as increased size for any lesion, the development of new lesions or neurological decline in otherwise stable patients. Recurrence was defined as reappearance of tumour in the brain on MRI. Blinding of outcome assessment is not described, but standardised assessment was applied to all patients.

A total of 333 patients were enrolled, with two patients (0.6%) subsequently excluded, leaving a sample of 331 patients—164 in the SRS plus WBRT arm, and 167 in the WBRT arm. However, it should be noted that 31 patients in the SRS plus WBRT arm (31%) did not undergo SRS. Radiosurgery was delivered either by Gamma Knife or Linac, but the proportion of Gamma Knife versus Linac patients could not be ascertained from the paper. The treatment groups appeared to be balanced on such variables as age, size of largest metastasis, primary tumour site, neurological function, recursive partitioning analysis (RPA) class, KPS, control of primary site, extracranial metastases, number of brain metastases, and MMSE score, but statistical comparisons are not presented.

#### **Survival: SRS plus WBRT versus WBRT alone**

On the primary outcome measure of overall survival, Andrews et al (2004) reported no statistically significant difference in mean survival between the group receiving SRS as a boost to WBRT (5.7 months) and the group receiving WBRT alone (6.5) ( $p = 0.14$ ). However, in examining the subgroup of patients with a single metastasis, it was found that patients receiving SRS boost ( $n = 92$ ) had significantly longer survival than those receiving WBRT alone ( $n = 94$ ). Mean survival for the SRS group was 6.5 months, compared with 4.9 months for the WBRT alone group ( $p = 0.04$ ).

Survival was examined in seven other subgroups, with an adjusted significance level used to take multiple comparisons into account. No association was found between SRS boost and improved survival in any of these subgroups.

#### **Survival: Gamma Knife versus Linac radiosurgery**

A non-randomised comparison between Gamma Knife and Linac radiosurgery was undertaken within the SRS plus WBRT treatment arm. No significant difference in survival was detected between these treatment modalities ( $p = 0.94$ ). Mean survival was not reported for Gamma Knife versus Linac radiosurgery.

It should be stressed that this is not a randomised comparison, and the number of patients receiving SRS by each treatment modality cannot be determined.

#### **Tumour progression and local control: SRS plus WBRT versus WBRT alone**

No difference between the treatment groups was noted in terms of overall time to intracranial tumour progression reported by participating institutions ( $p = 0.13$ ). However, local control at one year was found to be significantly higher in the SRS plus WBRT group (82%) compared with the WBRT alone group (71%) when assessed at

central review ( $p = 0.01$ ). This was supported by better local control rates reported per institution in the SRS arm ( $p = 0.01$ ).

However, MRI results for 117 patients (35%) were considered to be deficient and were not assessed at three-month follow-up. A further 61 patients had died, leaving 78 MRI scans available for the SRS boost arm (47% of the total randomised), and 75 scans for the WBRT arm (46%). This represents a substantial loss to follow-up. Furthermore, no statistical adjustment was undertaken to take multiple comparisons into account. Hence, these results relating to tumour progression and local control should be interpreted with caution.

### **Performance measures: SRS plus WBRT versus WBRT alone**

The percentage of patients exhibiting an improvement in KPS at six months follow-up was significantly higher in the SRS plus WBRT group (13%) compared with the WBRT alone group (4%) ( $p = 0.03$ ). Additionally, the percentage of patients reporting a reduction in steroid use at six months was higher in those undergoing SRS boost (54%) than in those undergoing WBRT alone (33%) ( $p = 0.02$ ). No significant differences in mental status as measured by the MMSE were evident.

Just as for the results for tumour progression and local control, the reported improvements in performance measures in the SRS arm must be regarded as tentative given the large loss to follow-up in both treatment groups. In these analyses, 88 patients were not included in the SRS plus WBRT treatment group (for the assessment of steroid usage, 91 patients were not included), whereas 89 patients were lost to follow-up in the WBRT arm. This represents more than 50 per cent of patients in both treatment groups. Furthermore, multiple comparisons elevate the probability of chance finding of statistical difference in these measures.

### **Discussion**

In general, the results from the RCT reported by Andrews et al (2004) are in accordance with the conclusions from previous systematic reviews. The addition of SRS as a boost to WBRT in patients with multiple brain metastases does not appear to improve overall survival compared with WBRT alone. However, this high-quality RCT has reported a small but statistically significant improvement in survival in patients with single metastases. Furthermore, although Andrews et al failed to demonstrate differences in time to progression, local control rates were higher for the SRS boost treatment group. Improvements in performance measures (KPS, steroid use) were also reported. However, these differences in local control and performance should be regarded as tentative given that the substantial loss to follow-up experienced in these analyses introduces the possibility of bias in the results, and the lack of statistical adjustment for multiple comparisons elevates the probability of chance statistical differences.

Although informative, this study does not directly address the specific WBRT comparator identified for this review (surgery plus WBRT). Postoperative patients were eligible for inclusion in this study, but the number of patients who had previously undergone surgery is not described. Hence, it is likely that a proportion of patients undergoing WBRT alone had previously undergone surgery, but this proportion cannot be ascertained. Similarly, it is likely that an unknown proportion of patients receiving SRS boost to WBRT had previously undergone surgery, a combination of treatments not identified as standard practice in Australia (see Appendix D). The applicability of these results to the Australian context is therefore uncertain.

The previous MSAC assessment concluded that there was insufficient evidence to allow a comparison between Gamma Knife and Linac-based radiosurgery. A subsequent systematic review concluded, based on cohort evidence, that there does not appear to be a difference between Gamma Knife and Linac radiosurgery in terms of local or distant brain relapse (Hailey 2002). The trial reported by Andrews et al (2004) allowed for a non-randomised comparison between Gamma Knife and Linac within the SRS boost arm, and found no difference between the technologies in terms of survival. This comparison is problematic, however. Of primary concern is the comparability of patients receiving Gamma Knife and those receiving Linac radiosurgery. The characteristics of these groups are not described or compared in the paper (including the number of patients undergoing each therapy). Treatment strategies for assigning patients to either technology, or differences between centres using either Gamma Knife or Linac devices, are not reported. Hence, it may be possible that differences in patient characteristics contribute to obscuring a difference in effectiveness between the treatments. However, given the almost identical survival curves for Gamma Knife and Linac radiosurgery, the comparability of the treatments in terms of survival is likely to be robust.

The outcome of quality of life was not addressed by a standardised instrument in this trial. Hence, the present review is unable to update the conclusions of the previous MSAC assessment or the systematic review by Hailey (2002) in this regard.

No evidence was identified that compared Gamma Knife with CyberKnife radiosurgery or with observation.

### **Conclusions**

There is Level II evidence that the addition of SRS to WBRT does not improve or decrease overall survival compared to WBRT alone in patients with multiple cerebral metastases. However, there is Level II evidence of a small but statistically significant improvement in survival when SRS is used as a boost to WBRT in patients with single metastases. SRS may lead to improvements in tumour control and patient performance in patients with up to three metastases; however, definitive conclusions are not possible.

There is Level III-2 evidence that there is no difference in overall survival between patients with multiple cerebral metastases treated by Gamma Knife versus Linac-based radiosurgery (in addition to WBRT).

There were no studies on which to base conclusions regarding the relative effectiveness of Gamma Knife and CyberKnife radiosurgery. Similarly, no conclusions are possible concerning a comparison between Gamma Knife radiosurgery and observation.

## **Arteriovenous Malformations**

### **Is it safe?**

#### **Previous MSAC assessment**

The previous MSAC review included 10 case series reports of surgery, 18 of Linac-based radiosurgery, and 12 of Gamma Knife radiosurgery, but noted the poor reporting and methodology of these studies. It was found that permanent neurological complications occurred in up to 15 per cent of surgical patients, compared with approximately 2 to

10 per cent of SRS patients. Little difference in event rates was evident between patients treated with Gamma Knife and Linac radiosurgery. However, it was concluded that methodological limitations, patient selection biases and inconsistencies in the reporting of adverse events prevented meaningful comparisons between the safety of Gamma Knife radiosurgery, surgery and Linac radiosurgery.

### **Systematic reviews, HTAs and practice guidelines**

The issue of safety has not been extensively addressed in other previous systematic reviews of Gamma Knife radiosurgery for AVMs. Hailey (2002) has noted that lower complication rates have been reported for SRS compared with other treatments, but states that these rates are not directly comparable since adverse events may be delayed and study follow-up is inadequate. There was some indication of increased risk of radiation-related complications in patients with previously unsuccessful treatment, but the quality of evidence was poor. Mitchell (2001) also noted the lack of long-term follow-up for adverse events, but reported that SRS appeared to be relatively safe, with a seven-year actuarial rate for persistent symptoms of 3.8 per cent. Comparative safety was uncertain.

### **Primary studies**

The present review was unable to identify comparative studies (either randomised or not randomised) of Gamma Knife radiosurgery and other treatments for AVMs. Case series studies were not reviewed due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret. These issues were identified in the previous MSAC report, which was unable to draw firm comparative safety conclusions on the basis of case series evidence.

### **Conclusions**

In the absence of additional comparative evidence since the completion of MSAC's previous assessment of Gamma Knife radiosurgery, this review is unable to update these conclusions. Event rates appear to be similar in patients treated with Gamma Knife and Linac radiosurgery, but methodological limitations, patient selection biases and inconsistencies in the reporting of adverse events prevented meaningful comparisons between the safety of Gamma Knife radiosurgery, surgery and Linac radiosurgery.

## **Is it effective?**

### **Previous MSAC assessment**

In the absence of controlled evidence of any kind, MSAC's previous assessment of Gamma Knife radiosurgery for AVMs included heterogeneous case series studies of poor methodological quality (MSAC 2001). The paucity of good-quality studies prohibited definitive conclusions regarding the place of radiosurgery in the treatment of AVMs, or on the relative effectiveness of Gamma Knife and Linac radiosurgery. However, it was noted that radiosurgery may be effective treatment for selected groups of patients, for example, those with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention.

## **Systematic reviews, HTAs and practice guidelines**

Four systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for AVMs. None of the reviews attempted a statistical synthesis of effectiveness data due to varying characteristics of the primary studies. None of the reviews identified RCTs of SRS for AVMs—each review provided summaries of cohort or case series evidence. MAS (2002) identified studies published since the previous MSAC review, but used the previous review as a basis for its conclusions. The other reviews overlapped to varying degrees with the previous MSAC review in terms of the primary studies included. None of the reviews provided sufficient information to meet all the specified criteria for high-quality reviews; however, Hailey (2002) was considered of good quality and had an extensive search strategy.

Only one review sought to specifically address the effectiveness of Gamma Knife radiosurgery, although this review also included Linac studies for the indication of AVMs (MAS 2002). Each of the other reviews, to varying degrees, reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery. Reviews also varied in the degree to which the population of interest to the current review was specifically addressed, with vascular malformations other than AVMs being included (AETMIS 2004). Table 14 describes the populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

### **Hailey 2002**

This systematic review addressed AVMs among other indications for Gamma Knife radiosurgery and, along with the previous MSAC assessment, provides the basis for the present update review. The review was generally of good quality, but although general inclusion criteria are described, criteria specific to each indication were not stated. A single reviewer applied the inclusion criteria and extracted data, and hence there were no validity checks on these methods. Additionally, the method of quality assessment of included studies was not described.

The review identified one cohort study comparing Gamma Knife radiosurgery and surgery, 13 case series using Gamma Knife radiosurgery, and 7 case series employing Linac-based radiosurgery. One of the Gamma Knife and two of the Linac case series were considered in the previous MSAC review. The authors note that it is difficult to draw firm conclusions regarding the effectiveness of SRS for AVMs in the absence of controlled trials. Issues of patient selection and methodological quality prevent comparisons between SRS and surgery. It is noted that SRS and surgery should be regarded as complimentary approaches, with surgery being preferred for lesions that can be ‘safely’ resected (however, appropriate patient selection remains controversial). Further, based on the case series studies identified, there was no indication that either Gamma Knife or Linac-based radiosurgery is superior to the other.

### **AETMIS 2004**

This systematic review, although published in English in 2004, was conducted in 2002 and was first published in French in the same year. Multiple indications are addressed, and among these are vascular malformations (including AVMs). Quality assessment of included studies is not described in this report. Inclusion criteria applied to primary studies, and the methods used to apply these criteria and extract data are not stated.

**Table 14 AVMs: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	21 studies: 1 cohort 20 case series	AVMs	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac, and surgery.	Not defined <i>a priori</i> . Considered obliteration and safety.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
AETMIS 2004	5 case series	Vascular lesions (including AVMs and cavernomas)	GK, Linac, helium ions, proton accelerator	Not defined <i>a priori</i> .	Not defined <i>a priori</i> .	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
MAS 2002	3 case series	AVMs	GK or Linac	Not defined <i>a priori</i> . Comparisons made between GK, Linac, and surgery.	Not defined <i>a priori</i> . Considered safety, and tumour control.	Specific inclusion criteria per indication not provided. Literature search was limited. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
Mitchell 2001	9 studies; 1 systematic review 8 case series	AVMs	SRS	Not defined <i>a priori</i> .	Safety and efficacy.	Specific inclusion criteria per indication not provided. Literature search was not described.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en sante; AVM = arteriovenous malformation; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; MAS = Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario; RCT = randomised controlled trial; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

A total of five case series were included (two of these were considered in the previous MSAC review). However, only one of these used Gamma Knife radiosurgery, and that was for patients with cavernomas rather than AVMs. No conclusions regarding the efficacy of SRS based on the included studies are presented. Statements are made noting that the efficacy of SRS is better in smaller AVMs, and that the optimal dose-effect relationship is still unknown; however, these are attributed to papers that were not included in the systematic review.

### MAS 2002

This 'rapid response HTA' updated the previous MSAC assessment of Gamma Knife radiosurgery by extending the search until April 2002. However, the search strategy was

not extensive, and it is possible that studies may have been missed. In addition, no inclusion criteria for primary studies were presented, the application of methods for the review was not described, and there was no discussion of the quality of the included studies.

Three case series using Gamma Knife radiosurgery published after the completion of the previous MSAC review were identified. Based on these studies and the conclusions of MSAC's prior assessment, it was found that there is no evidence for a difference in effectiveness between Gamma Knife and Linac radiosurgery in treating AVMs (however, no studies directly compared the technologies). Surgery was considered to be the best overall treatment for AVMs, but Gamma Knife radiosurgery was considered an important technology for surgically inaccessible AVMs or for those presenting significant surgical risk.

### **Mitchell 2001**

This brief review considered SRS compared with conventional techniques for patients with AVMs (among other indications), and updated a previous review published in 1998. The quality of the review cannot be assessed adequately, as information about inclusion criteria, the search strategy, application of methods, and detailed data from the included studies are not presented.

One included systematic review suggested that there was no reliable evidence indicating which patients may be eligible for SRS. The remaining eight case series (one of which was also included in the previous MSAC report) suggested that SRS may be useful in patients with AVMs that are difficult to treat by other methods, including those located in the brainstem, basal ganglia, thalamus, and very large AVMs or those incorporating aneurysms. However, overall it was found that the relative effectiveness of SRS and alternative treatments for AVMs remained uncertain, due to the absence of controlled studies.

### **Primary studies**

No primary studies were identified that compared Gamma Knife radiosurgery with alternative treatments in patients with AVMs.

### **Conclusions**

In the absence of comparative studies, this assessment is unable to update the findings of the previous MSAC review and the systematic review conducted by Hailey (2002). Gamma Knife radiosurgery should continue to be regarded as a complimentary approach to surgery in patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention. There is no evidence on which to base conclusions about the relative effectiveness of Gamma Knife, Linac and CyberKnife for the treatment of AVM.

## Acoustic neuroma

### Is it safe?

#### Previous MSAC assessment

MSAC's initial assessment of the safety of Gamma Knife radiosurgery for acoustic neuroma was hampered by poor reporting of complications, small sample sizes and methodological limitations of included studies. The review identified five case series addressing procedure-related morbidity and mortality for Gamma Knife radiosurgery, two case series addressing these outcomes for Linac radiosurgery, and four similar studies for surgery. The SRS series provided mortality information infrequently, and it was not clear whether this was because no death occurred or because it wasn't reported. Surgical complications were reported more extensively, with procedure-related mortality being less than one percent. Cerebrospinal fluid (CSF) leak was the most frequent surgical complication (10–25%). Meningitis occurred in 2 to 3 per cent of patients and resolved with antibiotics.

#### Systematic reviews, HTAs and practice guidelines

Systematic reviews of Gamma Knife radiosurgery for acoustic neuroma have noted that safety is difficult to address. Hailey (2002) quotes studies showing no mortality from Gamma Knife radiosurgery and overall complication rates of 20 per cent, with most being short term. Also noted is that other authors have concluded that surgery has a lower rate of complications compared with Gamma Knife radiosurgery, but that surgical complications included death. The HTA by AETMIS (2004) noted that the complications associated with surgery support the use of SRS as an alternative, although it is noted that a lack of standardisation in reporting complicates comparisons between treatments.

#### Primary studies

The literature search identified three comparative cohort studies investigating the safety of Gamma Knife radiosurgery for acoustic neuroma relative to surgery (these studies are described further in the following section, 'Is it effective?'). Case series studies were not considered due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret. These issues were identified in the previous MSAC report, which was unable to draw firm comparative safety conclusions on the basis of case series evidence. This section will concentrate on the safety outcomes of mortality and other treatment-related complications. The outcomes of hearing preservation, facial function and quality of life are addressed in the following section concerning the effectiveness of Gamma Knife radiosurgery.

In a retrospective cohort study, Myrseth et al (2005) compared complications associated with Gamma Knife radiosurgery with those after surgery. Mean follow-up was 5.9 years. The overall rate of treatment-related complications was reported to be 4 per cent for Gamma Knife radiosurgery, compared with 47 per cent for surgery ( $p < 0.0001$ ). The complications reported for Gamma Knife radiosurgery were symptomatic hydrocephalus in two patients (2%) and enlarged ventricles without hydrocephalus symptoms in a further two patients (2%). There was one death (from pulmonary embolus) among patients receiving surgery (1%). The most common postsurgical complication was CSF

leak (23 patients, 27%). Six patients had meningitis (7%), four patients had intracranial haematoma (5%), three had pneumonia (3%), two had subcutaneous abdominal haematoma from fat tissue harvesting (2%), and one patient each had pulmonary embolus and brainstem lesion (1% each).

Karpinos et al (2002) report a retrospective cohort study of patients undergoing Gamma Knife radiosurgery ( $n = 73$ ) or surgery ( $n = 23$ ) for acoustic neuroma, with mean follow-up of 46.7 months in Gamma Knife radiosurgery patients and 31 months for patients undergoing surgery. The overall rates of complications were similar to those reported by Myrseth et al (2005). Complications were reported in 5 per cent of Gamma Knife radiosurgery patients, compared with 48 per cent for the surgical group ( $p < 0.01$ ); however, the denominator used in calculating these rates is unclear. In the Gamma Knife radiosurgery group, three patients (4%) developed cystic necrosis of the tumour resulting in hydrocephalus, imbalance and nausea. Oedema occurred in three patients (4%) and diplopia in 2 (3%). Two patients died (one from metastatic prostate cancer, and one from acute myocardial infarction). The most common postoperative complication was imbalance in 10 patients (43%). Five patients each had CSF leak and infection (22% each), three had nausea (13%), two had oedema (9%), and one each had hydrocephalus, diplopia, seizure and intubation (4% each).

In a prospective cohort study with historical control by Regis et al (2002), a mortality rate of 1 per cent was reported for surgery (one patient with postoperative haematoma), compared with no deaths in those who received Gamma Knife radiosurgery. The most common postsurgical complication was CSF leakage, in eight patients (7%). Postoperative haematoma occurred in two patients (2%), brain trauma in a further two (2%), and meningitis in one (1%). These complications were not evident in the Gamma Knife radiosurgery group. Three patients who received Gamma Knife radiosurgery (3%) had hydrocephalus requiring a shunt, and one other patient (1%) had hydrocephalus secondary to post-treatment tumour growth. Pain was reported in 66 per cent of surgery patients, but pain was not evident in those receiving Gamma Knife radiosurgery.

## Discussion

The studies presented are somewhat inconsistent with Hailey's (2002) suggestion that surgery is reported to have lower complication rates than Gamma Knife radiosurgery. In two studies where direct comparison of overall rates of complications were possible, Gamma Knife radiosurgery was found to result in significantly fewer complications (4–5%) than surgery (47–48%) (Karpinos et al 2002; Myrseth et al 2005). Furthermore, two of these studies also reported no deaths after Gamma Knife radiosurgery, compared with a procedural mortality rate of around 1 per cent for surgery (Myrseth et al 2005; Regis et al 2002). Karpinos et al (2002) reported deaths in both Gamma Knife radiosurgery and surgical patients; however, it is unclear whether those deaths were treatment related.

The studies presented are consistent with the previous MSAC review in terms of the reported rates of complications after surgery. CSF leak appeared to be a common treatment-related complication after surgery; however, a slightly wider range was evident here than in the previous report (7–27%). Similarly, the rates of occurrence of meningitis had a wider range than previously reported (1–7%), although procedure-related mortality was consistent at around 1 percent.

The comparisons presented in these studies are problematic for a number of reasons. These are addressed in more depth in the following section ('Is it effective?'); however, most notable is that selection bias results in significant differences between Gamma Knife radiosurgery and surgical patients in terms of patient characteristics and prognostic factors. Two of the studies are retrospective and the other compares Gamma Knife radiosurgery with a historical surgery group, a design likely to overestimate differences in complication rates between the groups. Furthermore, the study by Karpinos et al (2002) includes a relative small group of patients undergoing surgery ( $n = 23$ ), and hence the complication rates derived from that study should be considered cautiously. The studies also reported follow-up that could be considered medium-term (with a mean of between approximately four and six years, where this could be ascertained). Additional follow-up is required before conclusions may be drawn about long-term treatment-related complications after Gamma Knife radiosurgery. Finally, these studies are insufficiently powered to investigate differences between treatments in terms of toxicity.

### **Conclusions**

There is Level III-2 and III-3 evidence that Gamma Knife radiosurgery appears to result in a lower rate of medium-term treatment-related complications and procedural mortality than does surgery. However, methodological limitations of these studies preclude conclusions regarding the magnitude of this effect. The relative long-term safety of Gamma Knife radiosurgery and surgery could not be assessed. There was no evidence on which to base a comparison between Gamma Knife and other forms of SRS (Linac and CyberKnife).

## **Is it effective?**

### **Previous MSAC assessment**

Controlled studies (RCTs, cohort studies, case-control studies) comparing Gamma Knife radiosurgery with other treatment options were not identified in MSAC's previous assessment (MSAC 2001). Hence, conclusions were based on case series evidence. Those studies were hampered by small sample sizes and methodological difficulties. It was concluded that radiosurgery offers similar outcomes in terms of tumour control to complete resection rates from surgery, particularly for patients with relatively small tumours. Similar outcomes of hearing preservation and facial function were observed between Gamma Knife radiosurgery and surgery series. However, it was noted that outcomes are likely to depend more on treatment team expertise, quality of imaging and treatment planning than on treatment modality (Gamma Knife or Linac radiosurgery, surgery). There appeared to be little difference between Gamma Knife and Linac radiosurgery, although definitive conclusions were not possible. Finally, it was noted that radiosurgery may be an effective treatment for selected groups of patients, for example, those with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention.

### **Systematic reviews, HTAs and practice guidelines**

Five systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for treating acoustic neuromas. One of the reviews combined patient numbers and event rates from different studies (Yamakami et al 2003); however, none of the other reviews attempted a statistical synthesis of

effectiveness data due to the varying characteristics of the primary studies. None of the reviews identified RCTs of SRS for acoustic neuromas; each review provided summaries of cohort or case series evidence. Mitchell (2001) has no overlap of studies with either this or the previous MSAC review; the rest of the reviews overlap in terms of the primary studies included to varying degrees. MAS (2002) identified studies published since the previous MSAC review, but used the previous review as a basis for its conclusions. None of the reviews provided sufficient information to meet all the specified criteria for high-quality reviews; however, Hailey (2002) was considered to be of good quality, and due to an extensive search strategy was unlikely to have missed potentially eligible studies.

Two reviews sought to specifically address the effectiveness of Gamma Knife radiosurgery (MAS 2002; Yamakami et al 2003). Each of the other reviews, to varying degrees, reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery. Table 15 describes the populations, types of SRS, effectiveness outcomes addressed and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

### **Hailey 2002**

Acoustic neuroma was addressed in this review, among other indications. Along with the previous MSAC assessment, it provides the basis for the present update review. The review was generally of good quality. General inclusion criteria are described; however, criteria specific to each indication were not stated. A single reviewer applied the inclusion criteria and extracted data, and hence there were no validity checks on these methods. Additionally, the method of quality assessment of included studies was not described.

One cohort study comparing Gamma Knife radiosurgery and fractionated stereotactic radiotherapy was identified, along with 17 case series investigating Gamma Knife and 5 case series of Linac radiosurgery. Three of the Linac case series were considered in the previous MSAC assessment. One of the Gamma Knife case series was also considered in the previous review, and two appeared to be later publications of studies considered previously including overlapping patients. The authors state that the methodological quality of the evidence is weak, and follow-up is limited. It was concluded that surgery remains the treatment of choice for many patients, but that SRS is useful where surgery is deemed to have an unacceptable risk or is refused by the patient. There was no clear evidence that any radiotherapy or radiosurgery treatment was superior to any other.

### **AETMIS 2004**

Acoustic neuroma is addressed along with other indications for SRS in this HTA report. Quality assessment of included studies is not described. Inclusion criteria applied to primary studies and the methods used to apply these criteria and extract data are not stated.

**Table 15 Acoustic neuroma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	2 studies: 1 cohort 22 case series	Acoustic neuroma	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac, and FSRT.	Not defined <i>a priori</i> . Considered tumour control, hearing preservation, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
AETMIS 2004	9 case series	Acoustic neuroma	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered tumour control and complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
Yamakami et al 2003	38 case series	Acoustic neuroma	GK	Surgery, conservative management	Not defined <i>a priori</i> . Hearing preservation, tumour progression, facial function, rate of surgery, tumour recurrence, mortality, major disability.	Literature search was limited. Study validity assessed in text, but method of quality assessment unclear. Comparisons between treatments are problematic.
MAS 2002	1 case series	Acoustic neuroma	Linac	Not defined <i>a priori</i> . Comparisons made between GK, Linac, and surgery.	Not defined <i>a priori</i> . Considered safety and efficacy.	Specific inclusion criteria per indication not provided. Literature search was limited. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.
Mitchell 2001	2 studies: 1 systematic review 1 case series	Acoustic neuroma	SRS	Not defined <i>a priori</i> .	Safety and efficacy. Specifically considered local control.	Specific inclusion criteria per indication not provided. Literature search was not described.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en santé; FSRT = fractionated stereotactic radiotherapy; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; MAS = Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario; SRS = stereotactic radiosurgery.

A total of nine case series studies were included in the review, six concerning Gamma Knife radiosurgery and three concerning Linac radiosurgery (with three of the Gamma Knife series also included in the previous MSAC review). It is unclear how the included

studies informed the conclusions of the AETMIS review. The authors reference a previous meta-analysis that warns against attributing advantages to SRS compared with other treatments due to methodological issues. The report states, however, that SRS could be an alternative to surgery or radiotherapy based on its relative precision and safety, and that Gamma Knife radiosurgery in particular may overcome some of the difficulties inherent in other standard treatments. The basis for these conclusions is unclear.

### **Yamakami et al 2003**

This review considered Gamma Knife radiosurgery specifically compared with surgery and conservative management. The search strategy was minimal, with limited search terms being applied to only one database, and the method of quality assessment of the included studies was unclear.

A total of 38 case series studies were included in the review, with 9 addressing Gamma Knife radiosurgery (1,475 patients), 16 addressing surgery (5,005 patients), and 13 considering conservative management (903 patients). Patients from studies of each intervention were combined to give overall event rates for different outcomes of interest. Rates of useful hearing preservation were found to be significantly higher among patients undergoing Gamma Knife radiosurgery (66%) than those undergoing surgery for either small-to-medium tumours (49%,  $p < 0.0001$ ) or tumours of any size (36%,  $p < 0.0001$ ), or those undergoing conservative management (37%,  $p < 0.0001$ ). Tumours treated with Gamma Knife radiosurgery were also significantly less likely to progress and more likely to regress than those managed conservatively ( $p < 0.0001$ ). However, these comparisons between treatments are problematic due to likely selection bias. The mean age of patients treated conservatively was five years older than those treated by Gamma Knife radiosurgery, and 15 years older than those undergoing surgery. It also seemed that the conservative management group had smaller tumours than the other patients. It is also noted in the review that the length of follow-up for the Gamma Knife radiosurgery studies is inadequate to assess its long-term effectiveness. Therefore, it is difficult to draw comparative conclusions from this review.

### **MAS 2002**

This ‘rapid response HTA’ updated the previous MSAC assessment of Gamma Knife radiosurgery by extending the search until April 2002. However, the search strategy was not extensive, and it is possible that studies may have been missed. In addition, no inclusion criteria for primary studies were presented, the application of methods for the review was not described, and there was no discussion of the quality of the included studies.

One case series report using Linac-based radiosurgery was identified as being published since the previous MSAC review. The report concluded that surgery is the best overall treatment for acoustic neuroma, but that SRS may have a role for surgically inaccessible tumours or those presenting an unacceptable surgical risk. There was no evidence of a difference in effectiveness between Gamma Knife and Linac radiosurgery, although fewer facial nerve complications were observed in patients treated with fractionated Linac-based radiosurgery.

### **Mitchell 2001**

This brief review considered SRS compared with “conventional techniques” for patients with acoustic neuromas (among other indications), and updated a previous review

published in 1998. The quality of the review cannot be assessed adequately, as information about inclusion criteria, the search strategy, application of methods, and detailed data from the included studies are not presented.

One systematic review and one case series report were included in the review. No comparative studies were included in the systematic review discussed in this report, and the quality of evidence was noted to be poor. It was tentatively noted that SRS seemed to have good rates of local control and acceptable longer term outcomes.

### **Primary studies**

No RCTs were identified that compared Gamma Knife radiosurgery with microsurgery in patients with acoustic neuroma. As such, the literature search attempted to identify non-randomised comparative studies. The search identified three cohort studies comparing Gamma Knife radiosurgery with surgery in acoustic neuroma patients.

### **Gamma Knife radiosurgery versus surgery**

Myrseth et al (2005) report a retrospective cohort study in 189 consecutive Norwegian patients, comparing Gamma Knife radiosurgery ( $n = 103$ ) with surgery ( $n = 86$ ). Treatment was allocated by patient preference, but Gamma Knife radiosurgery was recommended for elderly patients, those with serious additional disease, or in cases where hearing preservation was particularly crucial for occupational or social reasons. As a result of such differential treatment strategies, there were significant differences between the groups in pre-treatment patient characteristics. Patients receiving Gamma Knife radiosurgery were significantly older and less likely to have pre-treatment hearing deficit. The treatment groups also differed in tumour size, with Gamma Knife radiosurgery patients more likely to have tumours with a diameter of 11 to 20 mm. The mean follow-up was 5.9 years, and that did not differ significantly between the groups. The groups appeared to be balanced on pre-treatment tinnitus, vertigo, and trigeminal affection.

In terms of tumour control, Myrseth et al (2005) found no difference between Gamma Knife radiosurgery (89.2%) and surgery (94.2%) at follow-up ( $p = 0.2$ ). However, facial function was found to be significantly better in the Gamma Knife radiosurgery group, with 94.7 per cent having a House-Brackmann grade of 1 or 2, compared with 79.8 per cent of surgery patients ( $p = 0.003$ ). Quality of life was measured by both the SF-36 and the Glasgow Benefit Inventory. Results from the SF-36 were compared with Norwegian norms, and Gamma Knife radiosurgery was found to have significantly lower deviations below norms for the domains of 'physical functioning' ( $p = 0.03$ ), 'role-physical' ( $p = 0.04$ ) and 'role-emotional' ( $p = 0.003$ ). No differences were noted in 'bodily pain', 'general health', 'vitality', 'social functioning' and 'mental health'. It was also reported that Gamma Knife radiosurgery patients scored significantly higher than surgical patients overall and on the 'general and psychosocial health' domain of the Glasgow Benefit Inventory. No differences were observed in the domains of 'social support' or 'physical health status'.

Karpinos et al (2002) conducted a cohort study with 96 retrospectively identified patients undergoing Gamma Knife radiosurgery ( $n = 73$ ) or surgery ( $n = 23$ ) for acoustic neuroma. Different eligibility criteria were applied for the two treatments, and as a result there were significant differences in patient characteristics between the groups. Gamma Knife radiosurgery patients were significantly younger and had significantly smaller tumours than patients undergoing surgery. Additionally, there appeared to be differences

in the mean length of follow-up between the two groups, with Gamma Knife radiosurgery patients followed for a mean of 46.7 months, compared with 31 months for surgical patients. However, a statistical comparison was not made.

In those patients with serial MRI scans available at follow-up, tumour control was not significantly different in the Gamma Knife radiosurgery group (91%) and the surgical group (100%) ( $p > 0.05$ ). There was no difference in the proportion of patients with serviceable hearing who retained this level of hearing after Gamma Knife radiosurgery (44%) or surgery (40%); however, this comparison was based on small patient numbers. A significantly greater proportion of Gamma Knife radiosurgery patients retained pre-treatment measurable hearing (57%) than did surgical patients (14%) ( $p = 0.01$ ). Furthermore, a significantly greater proportion of patients with some measurable hearing prior to surgery had complete hearing loss after treatment (86%) compared with similar patients undergoing Gamma Knife radiosurgery (35%) ( $p = 0.001$ ). Gamma Knife radiosurgery patients were more likely to have House-Brackmann grade I or II facial nerve function (77.6% versus 35.3%,  $p = 0.001$ ), and were less likely to develop facial neuropathy (6.1% versus 35.3%,  $p = 0.008$ ) than patients who received surgery. There were no differences in KPS between the groups, and no differences in patient satisfaction, as measured by single questions asking whether patients were satisfied with treatment or would recommend it to a friend under similar circumstances.

In addition to the problems with selection bias in this study, loss to follow-up was also an issue, with 24 Gamma Knife radiosurgery patients (33%) and five surgical patients (22%) reported as being lost to follow-up. Several analyses included fewer patients still in one or both treatment arms.

Regis et al (2002) prospectively enrolled a consecutive cohort of 97 patients to receive Gamma Knife radiosurgery, and compared this with a historical control group of 110 patients who underwent surgery for stage II or III acoustic neuroma. The Gamma Knife radiosurgery group was treated between 1992 and 1998, and the surgical group was treated between 1983 and 1990. A functional evaluation questionnaire which measured facial function, ocular symptoms, eating difficulties, balance, hearing, complications, and quality of life was completed by Gamma Knife radiosurgery patients after at least three years. Follow-up for surgical patients is not described. The treatment groups were matched on tumour size by the inclusion in the study of stage II and III patients only. In addition, the groups appeared to be balanced on age, gender, size of populations, and cranial nerve impairment. A preliminary analysis found that functional outcome did not differ between stage II and III patients, and hence they were considered together in the analysis.

In terms of facial function, the surgical group exhibited significantly higher rates of hemifacial spasm (29% versus 8%,  $p = 0.002$ ), subjective trigeminal symptoms (55% versus 20%,  $p < 0.0001$ ), and facial sensory disturbance in patients without preoperative trigeminal nerve deficit (29% versus 4%,  $p = 0.0009$ ) compared with the Gamma Knife radiosurgery group. The proportion of patients with no facial motor disturbance was 100 per cent in the Gamma Knife radiosurgery group, compared with 53 per cent in the surgical group ( $p < 0.0001$ ). In terms of ocular symptoms, 49 per cent of the Gamma Knife radiosurgery group reported no symptoms, compared with 17 per cent of the surgical group ( $p < 0.0001$ ). It was also reported that the proportion of patients with no postoperative facial palsy who had ocular problems was significantly lower after Gamma Knife radiosurgery (27%) than after surgery (up to 75%) ( $p < 0.0001$ ).

Regis et al (2002) reported no differences between the groups in terms of post-treatment balance. Similarly, no difference in chewing difficulties was observed between the groups; however, eating difficulties in the absence of clinical injury to the V or VII cranial nerves were less frequent after Gamma Knife radiosurgery (9%) than after surgery (28%) ( $p = 0.004$ ). Functional hearing preservation was significantly higher in the Gamma Knife radiosurgery group (40%) than in the surgical group as a whole (5%) ( $p < 0.0001$ ). However, hearing preservation was only attempted in 11 surgical patients; success was achieved in four cases (45%), a non-significant difference when compared with those treated by Gamma Knife radiosurgery.

Finally, in terms of general quality of life, it was found that a higher proportion of Gamma Knife radiosurgery patients reported no change in daily life (91% versus 61%,  $p = 0.0002$ ) and were able to return to their previous occupation (99% versus 66%,  $p = 0.0002$ ), while a significantly lower proportion of Gamma Knife radiosurgery patients reported psycho behavioural problems (24% versus 69%,  $p < 0.0001$ ).

## Discussion

In terms of the effectiveness results specifically identified as relevant to this review, the two studies investigating rates of tumour control found no difference between Gamma Knife radiosurgery and surgery (Karpinos et al 2002; Myrseth et al 2005), and that is in accordance with the findings of the previous MSAC assessment and other systematic reviews. All three studies found better facial function in Gamma Knife radiosurgery patients relative to those undergoing surgery, and both studies examining hearing preservation found a relative advantage for Gamma Knife radiosurgery (Karpinos et al 2002; Regis et al 2002). Two studies examining quality of life found higher levels of functioning in some areas among Gamma Knife radiosurgery patients than surgical patients, one study with validated instruments (Myrseth et al 2005) and another where validation was unavailable (Regis et al 2002). No studies were identified that compared Gamma Knife with either Linac or CyberKnife radiosurgery, or with no treatment. No studies addressed the outcome of survival.

The cohort studies presented here were generally of poor methodological quality. Issues with selection bias were apparent in most studies. Differential treatment strategies were applied to patients treated with Gamma Knife radiosurgery and surgery, with at least one study enrolling patients to the Gamma Knife arm who were deemed ineligible for surgery (Karpinos et al 2002). Such differences in treatment eligibility resulted in patient characteristics and prognostic factors being significantly different between groups (Karpinos et al 2002; Myrseth et al 2005), thus biasing comparisons made between the treatments. Furthermore, there were problems with patient attrition in the study by Karpinos et al (2002) which have the potential to introduce bias into the results, and this study also based analyses on subgroups with relatively few patients.

In addition, the study reported by Regis et al (2002), although relatively well conducted in terms of ensuring comparability in patient characteristics between groups, is problematic for several reasons. Primarily, there are interpretative difficulties associated with comparing Gamma Knife radiosurgery patients to those who underwent surgery up to 15 years previously due to the evolution of surgical techniques over this period (Black & Johnson 2004). Outcomes for patients undergoing surgery are likely to have improved since this cohort was treated. Thus, such comparisons are seriously compromised by the historical nature of the control group in this study, with the results likely to be more favourable to Gamma Knife radiosurgery than a similar study with concurrent controls.

Adding to the difficulty in interpreting this study is the fact that the questionnaire used to determine functional outcomes was originally published in French, and validation of the instrument was unable to be ascertained. Inconsistencies in translation were also apparent. For example, the description of results refers to patients having difficulties in 'chewing', whereas the translation of the questionnaire presented in the paper refers to 'swallowing'. Such discrepancies raise concerns regarding the interpretation of results based on this questionnaire in an Australian context. Finally, the questionnaire-based nature of this study also leaves the results open to recall bias, and in the absence of information on the length of follow-up for the surgical group, this possibility cannot be discounted.

## Conclusions

Due to the methodological quality of the Level III-2 and Level III-3 evidence identified by the current review, it remains difficult to draw firm conclusions regarding the relative effectiveness of Gamma Knife radiosurgery compared with surgery for the treatment of acoustic neuroma. It is not possible to advance the conclusions reported in the previous MSAC assessment. Gamma Knife radiosurgery appears to offer similar outcomes in terms of tumour control to those from surgery. Gamma Knife radiosurgery may offer some benefits in terms of quality of life, hearing preservation and facial function in selected patient groups for whom surgery is not indicated, but in the absence of randomised controlled studies there is considerable uncertainty in specifying the magnitude of benefit. No comparison between Gamma Knife and Linac-based radiosurgery was possible, and hence the tentative conclusion reported in the previous MSAC review of little difference between the modalities is still applicable. Further, there were no studies on which to base conclusions on the comparative effectiveness of Gamma Knife and CyberKnife radiosurgery.

## Primary malignant lesions

### Is it safe?

#### Systematic reviews, HTAs and practice guidelines

A high-quality systematic review by Tsao et al (2005b) considered the results of one RCT in abstract form (the full report by Souhami et al [2004] is considered in the following section), and five prospective cohort studies. The randomised trial is reported to have found that SRS (by Gamma Knife or Linac) as a boost to EBRT and chemotherapy (BCNU) resulted in an increased risk of late radiation-related toxicity (grade 3). Complications in prospective studies ranged from no significant acute or late toxicity to brain necrosis being present in up to 14 per cent of patients. An unspecified number of retrospective series reported a few cases of significant oedema or radiation necrosis. It was concluded that the addition of SRS as a boost to EBRT is associated with an increased risk of toxicity, ranging from significant oedema to radiation necrosis.

Hailey (2002) makes passing references to complications and toxicity in assessing SRS for gliomas; however, no conclusions are reported. It was noted that SRS may be associated with 'considerable' toxicity. Somewhat in contrast to those reports, a review by AETMIS (2004) found SRS to be safe as an adjuvant treatment for gliomas, based on the results of seven case series studies. This review was completed prior to the publication of the RCT.

## Primary studies

The literature search identified one RCT investigating the safety of SRS (by Gamma Knife or Linac) in patients with glioblastoma multiforme (Souhami et al 2004). The trial considered SRS as a boost to EBRT compared with EBRT alone. BCNU was also administered in both arms. Acute and late radiation-related toxicities were recorded according to the grading scheme developed by the RTOG and the European Organisation for Research in the Treatment of Cancer (EORTC); however, only late toxicities are described in the report. At a median follow-up of 61 months, the overall late radiation-related complication rates for the groups treated with SRS boost (29%) and without SRS (26%) are not significantly different ( $p = 0.36$ ). However, it was found that grade 3 toxicity was evident in four patients after SRS (5%), three with neurologic toxicity, and one categorised as 'other'. Grade 3 neurologic toxicity is defined as seizures or paralysis, or coma (RTOG/EORTC 2005). Reporting in this study is somewhat inconsistent, but it seems that no grade 3 toxicity was evident for the treatment arm that did not include SRS. No grade 4 toxicities were reported in either treatment arm.

## Discussion

Based on the results reported by Souhami et al (2004), it can be noted that the addition of SRS to conventional radiotherapy plus BCNU results in rates of late radiation-related complications that are similar to conventional radiotherapy and chemotherapy alone. However, late complications appeared to be more severe with the addition of SRS, with a slightly increase risk of RTOG/EORTC grade 3 toxicities. This interpretation is consistent with a previous systematic review (Tsao et al 2005b). The delivery of SRS in this trial was primarily Linac-based, with roughly 40 per cent of patients receiving Gamma Knife-based treatment (for further discussion, see the following section 'Is it effective?'). Therefore, the degree to which these findings may be applied specifically to Gamma Knife radiosurgery is not clear. Although clinical comparisons between Gamma Knife and Linac radiosurgery patients were made in this trial, no such analyses were conducted for safety outcomes. This study is also insufficiently powered to detect differences between treatments in terms of safety outcomes, and therefore it is possible that more pronounced differences between treatments could become evident with larger sample sizes.

No studies were identified that compared the safety of Gamma Knife and CyberKnife radiosurgery. Case series studies reporting safety outcomes were not considered due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret.

## Conclusions

There is Level II evidence that the addition of SRS to conventional radiotherapy plus chemotherapy (BCNU) results in a slightly increased risk of late grade 3 radiation-related toxicity compared with EBRT and BCNU alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. No conclusions about the relative safety of Gamma Knife and alternative forms of SRS (Linac and CyberKnife) are possible.

## Is it effective?

### **Systematic reviews, HTAs and practice guidelines**

Four systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for primary malignant lesions. None of the reviews attempted a statistical synthesis of effectiveness data due to varying characteristics of the primary studies. Two of the reviews identified an RCT of SRS for primary malignant lesions (Laperriere, Perry, & Zuraw 2004; Tsao et al 2005b), reported in either abstract or full publication form. This trial is also considered in the current MSAC review. The two other reviews provided summaries of case series evidence alone. None of the reviews provided sufficient information to meet all the specified criteria for high-quality reviews; however, Hailey (2002) was considered to be of good quality, and due to an extensive search strategy was unlikely to have missed potentially eligible studies.

Each of the reviews, to varying degrees, reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery. The patient populations also differed between reviews. Three reviews focussed on malignant gliomas (AETMIS 2004; Laperriere, Perry, & Zuraw 2004; Tsao et al 2005b), while the review by Hailey (2002) included studies addressing other types of primary malignant tumour, and some studies included patients who had benign lesions. Table 16 describes the populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

#### **Hailey 2002**

This review examined primary malignant lesions, among other indications. Although of generally good quality, inclusion criteria specific to each indication were not stated, no validation of the application of inclusion criteria or data extraction were undertaken, and the method of quality assessment of included studies was not described. However, the search strategy was extensive, and as such Hailey (2002) provides the basis for the present update review.

Eight case series of Gamma Knife radiosurgery, and four case series and one cohort using Linac-based radiotherapy were identified. Patients in these studies had a variety of lesions, including malignant gliomas, craniopharyngiomas and ependymomas. Some included patients who had benign lesions. Only limited conclusions were possible. It was noted that those studies reporting on the treatment of gliomas indicated limited success of SRS. Two of the studies included children and 'useful' results were obtained for some types of tumour. However, no conclusions on the comparative efficacy of SRS and alternative treatments were made, although it was suggested that phase III trials of SRS against conventional treatments would be unlikely to demonstrate differences in survival.

#### **Tsao et al 2005b**

This paper on behalf of ASTRO presents a high-quality systematic review of the evidence for radiosurgery for malignant glioma. Fractionated stereotactic radiotherapy was addressed along with SRS; however, those results are not presented here. One RCT was identified which compared SRS (by Gamma Knife or Linac radiosurgery) plus surgery and external beam radiotherapy (EBRT) against surgery plus EBRT (Souhami et al 2004). This trial is also included in the present MSAC assessment and is discussed in detail in the following section. In addition, five prospective cohort studies and seven retrospective series were identified that compared these treatment strategies.

In terms of survival, the review conclusions are based on the results of the RCT which provided no evidence for improved survival in patients undergoing SRS in addition to surgery, EBRT and BCNU chemotherapy, compared with those undergoing surgery, EBRT and BCNU. In addition, that trial found no difference between the treatment strategies in terms of patterns of failure. The evidence from additional studies concerning brain control or tumour response was found to be of poor quality, with selection bias evident and no direct comparisons between patients treated with radiosurgery boost and those without. Hence, there was insufficient evidence to demonstrate improved brain control or tumour response in patients with newly diagnosed malignant glioma undergoing SRS in addition to surgery and EBRT.

The RCT found no benefit of the addition of SRS in terms of quality of life, and the additional studies considered in the review corroborated that finding.

**Table 16 Primary malignant lesions: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	13 studies: 1 cohort 12 case series	Primary malignant lesions	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered survival, tumour control, tumour response, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
Tsao et al 2005b	13 studies: 1 RCT 12 cohorts or case series	Adult patients with high-grade glioma: glioblastoma multiforme, anaplastic astrocytoma, mixed anaplastic oligoastrocytoma, anaplastic oligodendroglioma.	Single fraction SRS (plus surgery and EBRT)	Surgery plus EBRT	Survival, quality of life or symptom control, tumour control or response, toxicity.	Study validity assessed in text, but method of quality assessment unclear.
Laperriere, Perry & Zuraw 2004	1 RCT	Newly diagnosed adults with histologic confirmation of glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma.	SRS (plus surgery, EBRT and BCNU)	Surgery, EBRT and BCNU	Survival	Literature search was limited. Study validity assessed in text, but method of quality assessment unclear. Insufficient detail of primary study presented.
AETMIS 2004	7 case series	Gliomas	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered survival, reintervention, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en santé; BCNU = a proprietary form of the drug carmustine; EBRT = external-beam radiotherapy; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

### **Laperriere, Perry & Zuraw 2004**

Published by the Program in Evidence-Based Care in Canada, this systematic review forms the basis for a practice guideline on radiotherapy for newly diagnosed malignant glioma in adults. The review was completed in 2000 and updated in June 2004. SRS was addressed among a number of radiotherapeutic interventions. Only the conclusions regarding SRS are described here. The report is based on a somewhat limited search (Medline and the Cochrane library only), and although the validity of included studies is discussed in the text, the methods employed for quality assessment are unclear. Furthermore, there is insufficient detail provided about the included studies.

Eleven studies were included in the original review; however, no conclusions were possible given the absence of RCTs. The update identified one RCT, presented in preliminary abstract form, the full publication of which is also considered here (Souhami et al 2004). That trial found no significant differences in median survival, patterns of failure, quality of life or mental status between patients with or without SRS in addition to surgery, EBRT and BCNU. It was therefore recommended that postoperative EBRT should be standard therapy for patients with newly diagnosed malignant glioma.

### **AETMIS 2004**

Primary malignant lesions, specifically gliomas, were addressed, along with other indications for SRS in this HTA report. Quality assessment, inclusion criteria, and methods used to apply these criteria and extract data are not stated.

Seven case series studies were included in this review, with two addressing Gamma Knife and five addressing Linac-based radiosurgery. The reported efficacy for gliomas was found to vary widely. Despite the lack of comparative studies, SRS was described as a safe and effective adjuvant treatment that prolongs survival in patients with malignant gliomas. The comparative effectiveness of SRS and alternative treatments was not addressed.

### **Primary studies: Souhami et al 2004**

One RCT was identified as being published since the previous MSAC assessment and the HTA report by Hailey (2002). This multicentre trial conducted by RTOG (protocol 93-05) compared SRS (by Gamma Knife or Linac) in addition to EBRT and chemotherapy with BCNU and with EBRT and BCNU alone in patients with glioblastoma multiforme. The primary outcome of this study was survival, and secondary outcomes included severity of toxicities, neurological function and quality of life.

The quality of this trial was evaluated according to the checklist developed by the NHMRC (2000). Randomisation was of high quality, and was carried out by randomised permuted block within strata. Patients were stratified by age and KPS. Sample size calculations were based on a power of 80 per cent at  $\alpha = 0.05$  to detect a 50 per cent improvement in median survival from 12.5 to 18.75 months. The sample size estimated to detect this difference with the specified power was 200 patients.

The statistical methodology is well described. An intention to treat analysis was performed but was not presented in the paper, apart from mentioning that the intention to treat survival analysis was similar to the results described. Instead, randomised patients were excluded from the analysis due to anaplastic histology, refusal of therapy or withdrawn consent, prior chemotherapy, multifocal tumours, unrecorded KPS, and

tumours greater than 40 mm at the time of SRS. There were 17 post-randomisation exclusions (8%).

Blinding of outcome assessment was not described, but standardised assessment was applied to all patients. Patients completed the MMSE and the Spitzer QOL Index before therapy, during EBRT and at each follow-up visit to evaluate neurological function and quality of life. The frequency of follow-up visits is not stated; however, it is noted that contrast-enhanced CT or MRI scans were done at three to four month intervals or at the time of neurological progression.

A total of 203 patients were enrolled, and with 17 exclusions, the sample size analysed was 186 patients, 89 in the SRS plus EBRT and BCNU arm, and 88 in the EBRT and BCNU arm. A quality assurance analysis of 79 patients in the SRS arm indicated that 18 per cent of patients had deviations from the protocol that were considered unacceptable (a further 22 per cent had acceptable protocol deviations). Radiosurgery was delivered by Gamma Knife and Linac radiosurgery. Roughly 40 per cent of SRS patients received Gamma Knife radiosurgery (this proportion is derived from a breakdown of 79 SRS patients which may or may not correspond to those included in the quality assessment analysis). Patients who had lesions greater than 40 mm in size were eligible for inclusion in this trial if the lesion was rendered less than or equal to 40 mm by surgical resection. It appears that approximately 90 per cent of patients in each treatment arm underwent prior surgical resection to debulk the lesion. The treatment groups appear to be well balanced on a number of pre-treatment characteristics, including age and KPS (these two variables being used to stratify the samples), as well as gender, race, neurological function, MMSE, RPA class, Spitzer QOL index, and education level. It appears as though tumour size tended to be smaller in the SRS group. However, the authors state that treatment groups were well balanced. The fact that statistical comparisons between groups in terms of pre-treatment characteristics are not presented means that this cannot be explored further.

#### **Survival: SRS plus EBRT and BCNU versus EBRT and BCNU alone**

For the primary outcome measure of survival, Souhami et al (2004) report no statistically significant differences in overall median survival time between the group receiving SRS in addition to EBRT and BCNU (13.5 months) compared with the group receiving EBRT and BCNU alone (13.6 months) ( $p = 0.57$ ). Similarly, comparisons between the SRS group and the EBRT and BCNU alone group revealed no statistically significant differences in two-year survival (21% versus 19%, respectively) or three-year survival (9% versus 13%, respectively) ( $p =$  not significant, exact  $p$  not reported). Subgroup analyses were conducted in patients with RPA class III or IV tumours, and in those who had a tumour size of less than 40 mm preoperatively, and no statistically significant differences in median survival between treatment groups were evident.

It was noted that an intention to treat survival analysis was also conducted, and that nearly identical results to those described here were obtained.

#### **Survival: Gamma Knife versus Linac radiosurgery**

A non-randomised comparison within the SRS treatment was made between patients receiving Gamma Knife and Linac-based radiosurgery. No significant difference was detected between these treatment modalities. The median survival time for Gamma Knife radiosurgery patients was 12.1 months, compared with 14.0 months for Linac

patients ( $p = 0.71$ ). Ten patients (11%) were excluded from the analysis, and the reasons for exclusion are not described.

No differences were observed between the study arms in patterns of treatment failure.

#### **Quality of life: SRS plus EBRT and BCNU versus EBRT and BCNU alone**

No differences were observed in quality of life based on the Spitzer QOL Index. Deterioration in quality of life between baseline and the end of treatment was observed in 49 per cent of patients undergoing SRS in addition to EBRT and BCNU, compared with 42 per cent of those receiving EBRT and BCNU alone ( $p = 0.70$ ).

Missing data was apparent for 40 patients in the SRS arm (45%) and 35 patients in the EBRT and BCNU alone arm (36%). The main reasons for missing data were reported to be omission of the pre-treatment questionnaire by the treating institution or completion of the baseline questionnaire after the initiation of therapy.

#### **Cognitive function: SRS plus EBRT and BCNU versus EBRT and BCNU alone**

No differences were observed in cognitive function based on the MMSE. Cognitive decline between baseline and three month follow-up was observed in 25 per cent of patients undergoing SRS in addition to EBRT and BCNU, compared with 35 per cent of those receiving EBRT and BCNU alone ( $p = 0.21$ ).

Missing data was apparent for 40 patients in the SRS arm (45%) and 38 patients in the EBRT and BCNU alone arm (39%) for the reasons described previously.

### **Discussion**

Two of the systematic reviews identified in this assessment (Laperriere, Perry & Zuraw 2004; Tsao et al 2005b) based their conclusions primarily on the RCT reported by Souhami et al (2004) and its finding that no survival advantage was evident in patients undergoing SRS in addition to EBRT and BCNU versus EBRT and BCNU alone. In addition, Tsao et al (2005b) describe cohort and case series evidence that support the results of the randomised trial, and based solely on case series evidence, the HTA report by Hailey (2002) concluded that trials would be unlikely to demonstrate a difference in survival between SRS and standard treatments. The AETMIS report (2004) is the only systematic review identified which has conclusions somewhat at odds with the RCT in terms of survival; however, this HTA was conducted two years prior to the trial's publication and does not address the comparative effectiveness of SRS.

The RTOG 93-05 trial has some features that limit its relevance to the research questions of this review. Firstly, although it appears as though roughly 40 per cent of SRS patients received Gamma Knife radiosurgery, data for all such patients are not presented, meaning that this could be as high as 47 per cent or as low as 36 per cent. Regardless, this trial does not meet the *a priori* eligibility criterion specified for this review that at least 75 per cent of SRS patients should receive Gamma Knife radiosurgery. The decision was made to include this study since it was the only RCT in the area, a substantial proportion of patients did receive Gamma Knife radiosurgery, and although problematic (see following) the comparison between Gamma Knife and Linac radiosurgery in this trial showed no difference in effectiveness between the two modalities. Furthermore, this comparison alone meets the eligibility criteria specified for cohort studies and would have been included in the review in any case.

Other features of this trial that have the potential to limit its applicability to the current review are the extent to which patients underwent prior surgery and chemotherapy. Clinical advice has suggested that surgery prior to EBRT (and SRS) is standard clinical practice in Australia (see Appendix D). It seems that approximately 10 per cent of patients in the RTOG 95-03 trial did not undergo prior surgery. Although not optimal, this is unlikely to pose a serious threat to generalisability of the results. With regard to treatment with chemotherapy, this is not described in the clinical flowchart presented in Appendix D, but clinical advice suggests that chemotherapy is commonly used in Australia for patients with gliomas (albeit more likely with temozolomide than BCNU). Therefore, the advisory panel considered the results of this study to be applicable to an Australian context.

Also, the fact that comparisons between Gamma Knife and Linac radiosurgery are not randomised, and hence may be subject to bias. Similar issues were addressed in the previous section addressing the indication of cerebral metastases. Although no differences in survival were found between patients receiving Gamma Knife and those receiving Linac-based radiosurgery, the comparability of the patients receiving either treatment is unknown. It remains possible that differences in patient characteristics may contribute to obscuring a difference in effectiveness between the treatments; however, given that observed differences did not approach statistical significance, this finding is likely to be robust.

### **Conclusions**

There is Level II evidence that the addition of SRS to EBRT, surgery and chemotherapy does not improve or decrease survival, neurological function or quality of life compared with EBRT, surgery and chemotherapy alone in patients with primary malignant lesions (glioblastoma multiforme). There is Level III-2 evidence that there is no difference in overall survival between patients treated by Gamma Knife versus Linac-based radiosurgery (in addition to surgery, EBRT and chemotherapy). No studies were identified that addressed the relative effectiveness of Gamma Knife and CyberKnife radiosurgery, and hence no conclusions may be drawn regarding comparisons between these forms of SRS.

## **Meningioma**

### **Is it safe?**

#### **Systematic reviews, HTAs and practice guidelines**

A systematic review conducted by AETMIS (2004) concluded that SRS (by Gamma Knife or Linac) is safe in treating meningiomas. However, the derivation of this conclusion remains unclear. Radiosurgery is noted to have a theoretical advantage over conventional radiotherapy in terms of toxicity, but the review includes series suggesting that neuropathies may occur with administered doses of greater than 19 Gy (or 10 Gy in the case of ophthalmic complications). Complications of SRS were noted to be mainly transient, but deaths have been reported in Linac-based series.

## Primary studies

The literature search identified three comparative cohort studies investigating the safety of Gamma Knife radiosurgery (with or without surgery) for meningiomas relative to surgery (these studies are described further in the following section, 'Is it effective?'). No RCTs were found. Case series studies were not reviewed due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret. This section considers treatment-related morbidity and mortality, along with radiation necrosis (another complication related to the procedure defined *a priori* as relevant to this review). The outcome of neurological functioning is considered in more detail under the section titled 'Is it effective?'

Linksey et al (2005) report a retrospective cohort of patients with meningiomas treated either by Gamma Knife radiosurgery or surgery. There was no procedure-related or 30-day mortality in either treatment group. One patient treated with surgery and Gamma Knife radiosurgery died after disease progression; however, that patient had malignant disease (as opposed to benign meningioma, which is the condition relevant to the present assessment). Three patients died of causes unrelated to treatment. Other complications were considered temporary, but the types of complications differed between the treatment groups. For Gamma Knife radiosurgery, the most common complication was focal scalp numbness from the stereotactic headframe pins (3 patients, 8%). Other complications included focal areas of scalp alopecia, temporary worsening of visual acuity or field, temporary hemiparesis and new seizures from transient peritumoural oedema (2 patients each, 5%), new cervical spinal cord syrinx, and outbreak of V<sub>1</sub> shingles (1 patient each, 3%). For surgery, the most common complication was temporary frontalis nerve paresis (3 patients, 9%). Other complications included deep venous thrombosis, persistent peri-incisional scalp numbness (2 patients each, 6%), epidural abscess, asymptomatic resection cavity haematoma, and bilateral temporal lobe HSV encephalitis two weeks postoperatively (1 patient each, 3%). There was no major permanent neurological morbidity in either group.

A retrospective cohort by Pollock et al (2003) also compared Gamma Knife radiosurgery with surgery, with a mean follow-up of approximately five years. Mortality was not reported. The rate of complications was higher in patients undergoing surgery (22%) than those undergoing Gamma Knife radiosurgery (10%), but this difference did not reach statistical significance ( $p = 0.06$ ). As reported by Linksey, Davis, & Ratanatharathorn (2005), the types of complications appeared to differ between the treatments. The most common complication after Gamma Knife radiosurgery was facial numbness/pain (3 patients, 5%). Other complications included new diplopia, cyst formation requiring placement of a cysto-peritoneal shunt, and stroke secondary to carotid artery occlusion after Gamma Knife radiosurgery for a cavernous sinus meningioma (1 patient each, 2%). The most common complication after surgery was cranial nerve deficit (21 patients, 15%). Other complications included, hemiparesis (4 patients, 3%), new seizures (2 patients, 1%), infection, subdural haematoma requiring evacuation, visual field loss, and craniotomy flap migration requiring cosmetic reconstruction (1 patient each, <1%).

In a small retrospective cohort study, Hart and Giannotta (2003) compared patients with meningiomas undergoing Gamma Knife radiosurgery in addition to surgery to those undergoing either single-sitting or staged surgical resection alone. Mean follow-up was 69.8 months. There were no statistically significant differences in rates of complications. One death (1%) due to ischaemic deficit from an encased posterior circulation vessel

occurred in the single-sitting surgery group, with no deaths after either Gamma Knife radiosurgery or staged surgery. Two patients in the single-sitting surgical group suffered major neurological impairment, one with hemiparesis and one with ataxia and cognitive dysfunction (11% each). No major neurological impairment was evident in the Gamma Knife radiosurgery plus surgery group or in the staged surgery alone group. Cranial nerve deficits in three patients were evident in the staged surgery group (33%), and consisted of permanent third, fourth, and eighth palsy. A fourth nerve palsy was evident after staged surgery alone (16%), and three patients (27%) had cranial nerve deficits after surgery plus Gamma Knife (a third, sixth, and eighth palsy), but these were reported to develop after surgery rather than after Gamma Knife treatment.

## **Discussion**

No deaths were reported after Gamma Knife radiosurgery in the included studies. Complications appear to be transitory in the short-to-medium term. Studies have reported that rates of complications do not differ between Gamma Knife radiosurgery and surgery, but that different adverse event profiles are apparent between the treatments. However, there are substantial methodological problems regarding the comparability of treatment groups within these studies that limit any conclusions of relative safety (such issues are described further under the section ‘Is it effective?’). It is also acknowledged by the authors of the included studies that the follow-up periods described are inadequate, particularly in assessing long-term radiosurgical complications. Furthermore, the study reported by Hart and Giannotta (2003) is small, and as such is of only limited value in informing conclusions. However, none of the studies are adequately powered to investigate differences in safety between treatments.

The outcome of radiation necrosis is not reported in any of the included studies, and there are no studies on which to base comparisons between Gamma Knife radiosurgery (with or without surgery), or between different types of SRS (Gamma Knife, Linac, CyberKnife).

## **Conclusions**

Due to methodological limitations of the included Level III-2 studies, it is not possible to draw definitive conclusion regarding the relative safety of Gamma Knife radiosurgery and surgery. Complications after Gamma Knife radiosurgery tend to be transitory in the short-to-medium term, but inadequate follow-up precludes conclusions about long-term safety. A lack of comparative evidence further precludes conclusions regarding the relative safety of Gamma Knife and conventional radiotherapy (alone or combination with surgery), and other forms of SRS (Linac, CyberKnife).

## **Is it effective?**

### **Systematic reviews, HTAs and practice guidelines**

Two systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for meningiomas. Neither review attempted a statistical synthesis of effectiveness data. Both reviews provided summaries of case series evidence alone (none of these studies were eligible for inclusion in the current MSAC review). None of the reviews provided sufficient information to meet all the specified criteria for high-quality reviews; however, Hailey (2002) was considered to be of

good quality, and due to an extensive search strategy was unlikely to have missed potentially eligible studies.

**Table 17 Meningioma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	21 case series	Meningiomas	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered progression, neurological symptoms, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
AETMIS 2004	10 case series	Meningiomas	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered tumour control, functional status, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en santé; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

Each of the reviews reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery. Table 17 describes the populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

### Hailey 2002

This review examined meningiomas, among other indications. Although of generally good quality, inclusion criteria specific to each indication were not stated, no validation of the application of inclusion criteria or data extraction were undertaken, and the method of quality assessment of included studies was not described. The search strategy was extensive, however, and this review is unlikely to have missed relevant studies. Hence, Hailey (2002) provides the basis for the present update review.

Fifteen case series of Gamma Knife and six case series of Linac radiosurgery were included in this review. These papers were found to indicate benefit for patients undergoing SRS in terms of tumour control and neurological symptom improvement. However, the authors note that the included studies are heterogeneous in terms of the populations and clinical situations described, and as such, no meaningful comparisons can be made between SRS and other treatments, or between types of SRS.

### AETMIS 2004

Meningiomas were addressed along with other indications for SRS in this HTA report. Quality assessment, inclusion criteria, and methods used to apply these criteria and extract data are not stated.

The results of four case series addressing Gamma Knife and six case series addressing Linac radiosurgery were described. Based on these results it is stated that Gamma Knife radiosurgery provides better tumour growth control (87–100%) and improved functional status (87–92%) compared with surgery and conventional radiotherapy, alone or in combination. Rates of tumour progression were found to be similar between the Gamma Knife and Linac radiosurgery series. It was concluded that SRS by either Gamma Knife or Linac is effective in controlling meningiomas, but that studies indicate that outcomes depend on tumour characteristics.

It is unclear how this conclusion comparing the effectiveness of Gamma Knife radiosurgery and other treatments (surgery, conventional radiotherapy) was derived, since none of the included studies compared those treatments, and no series employing surgery or conventional radiotherapy for meningiomas were described.

### **Primary studies**

No RCTs were identified that compared Gamma Knife radiosurgery with the comparator treatments in patients with meningiomas. As such, the literature search attempted to identify non-randomised comparative studies. The search identified two cohort studies comparing Gamma Knife radiosurgery with surgery, and one cohort study comparing surgery plus Gamma Knife radiosurgery with surgery alone.

### **Gamma Knife radiosurgery versus surgery**

Linskey, Davis, & Ratanatharathorn (2005) report a retrospective cohort of 64 consecutive meningioma patients. The results of this paper are presented by number of operations rather than by number of patients (some patients with more than one lesion had multiple procedures). The total number of operations was 73, with Gamma Knife radiosurgery being performed in 38, and surgery in 35 (stereotactic biopsy was performed in one further patient). The histological status of these lesions was determined, with 61 being benign and 12 being malignant or atypical. An analysis of tumour location implied that different treatment allocation approaches were applied to Gamma Knife radiosurgery and surgery. Tumours arising from the convexity, sphenoidal ridge without cavernous sinus involvement, and the posterior fossa were more likely to undergo surgery. Cavernous sinus and petroclival tumours as well as those involving the Torcular herophili were more likely to undergo Gamma Knife radiosurgery. Additionally, 17 surgical patients (49%) had tumours too large for treatment by Gamma Knife radiosurgery. There were significant differences between the treatment groups in patient characteristics and prognostic variables. Gamma Knife radiosurgery patients were significantly older and were more likely to have had failed previous treatment than were surgery patients. Mean tumour volume and KPS were both significantly lower in the Gamma Knife radiosurgery group. The treatment groups appeared to be balanced on gender and histological status. Patients were followed up for a median of two years.

Tumour progression was considered in both benign and malignant/atypical patients. No statistically significant differences were observed between treatment groups. For benign lesions, there was no difference in the rate of tumour recurrence at follow-up between Gamma Knife radiosurgery (3.2%) and surgery overall (6.7%), or grade 1 or 2 resections (0.0%). No difference was observed between treatment with Gamma Knife radiosurgery and surgery in the percentage of patients with worsening neurological symptoms after treatment (13% versus 14%, respectively). However, Gamma Knife radiosurgery patients were significantly more likely to have improved neurological function (43%) compared with surgery patients, and neurological symptoms were more likely to remain unchanged

in surgical patients (63%) than in Gamma Knife radiosurgery patients (43%) ( $p < 0.0001$ ). Satisfaction with treatment was high and not significantly different between treatment groups, with 91% and 92 per cent of Gamma Knife radiosurgery and surgery patients (respectively) indicating they were satisfied and would recommend the procedure to a friend in similar circumstances.

Pollock et al (2003) undertook a retrospective cohort study with 198 consecutive patients with benign meningiomas measuring less than 35 mm in average diameter. A total of 62 patients underwent Gamma Knife radiosurgery and 136 underwent surgery. The method for allocating the two treatments was not described, but patients with skull base lesions were significantly more likely to undergo Gamma Knife radiosurgery, and those with convexity location were significantly more likely to undergo surgery. Gamma Knife radiosurgery patients were significantly older and were more likely to have had preoperative cranial nerve deficit, while surgical patients were more likely to have had preoperative seizure. The treatment groups appear to be balanced on gender, tumour size and length of follow-up. The mean follow-up for Gamma Knife radiosurgery (63.5 months) was not significantly different to that for surgery (64.2 months).

Overall, a significantly lower percentage of Gamma Knife radiosurgery patients experienced tumour recurrence (2%) than did patients undergoing surgery (11%) ( $p = 0.04$ ). Progression-free survival was examined according to resection grade. No differences in three- and seven-year survival between Gamma Knife radiosurgery (100% and 95%, respectively) and grade 1 resections (100% and 96%, respectively) were observed ( $p = 0.09$ ). Three- and seven-year survival was found to be significantly lower in grade 2 resections (91% and 82%, respectively) ( $p < 0.05$ ), and in grades 3 or 4 resections (68% and 34%, respectively) ( $p < 0.001$ ). Fewer Gamma Knife radiosurgery patients required additional treatment (3%) than did surgical patients (13%) ( $p = 0.02$ ). There were no differences in the rates of symptom improvement between the Gamma Knife radiosurgery (13%) and surgical groups (13%).

### **Surgery plus Gamma Knife radiosurgery versus surgery alone**

Hart and Giannotta (2003) conducted a retrospective cohort study of 26 consecutive patients undergoing surgery with or without Gamma Knife radiosurgery. Patients had large, non-compartmental meningiomas measuring at least 4 cm in one or more linear dimension. Eleven patients underwent Gamma Knife radiosurgery between eight and 12 weeks after surgery. The aim of surgery in these patients was cytoreduction, with the residual tumour volume treatable by Gamma Knife radiosurgery. The remaining 15 patients underwent surgery, either in a single sitting ( $n = 9$ ) or by a staged procedure ( $n = 6$ ). The aim of single sitting surgery was gross total resection, while staged surgery aimed for maximal debulking, leaving only residual tumour that could be reached from a different corridor. Demographics and other patient characteristics are not described, and comparability of the groups is not discussed in the report, hence it is not possible to determine whether the treatment groups differed on important prognostic variables. The mean radiographic follow-up of tumour progression was 69.8 months.

In terms of tumour progression, cranial nerve deficits and major neurological deficits, no statistically significant differences were observed between the surgery plus Gamma Knife radiosurgery group compared with either the single sitting or multiple sitting surgery groups, or the surgical groups combined. Two patients in the Gamma Knife radiosurgery group had tumour recurrence (18%) compared with none of the surgical patients. Cranial nerve deficits were observed in 27 per cent of the Gamma Knife radiosurgery group

(3/11 patients), compared with 33 per cent in the single sitting surgical group (3/9 patients), and 16 per cent in the staged surgical group (1/6 patients). Major neurological deficits occurred in 22 per cent of the single sitting surgery group (2/9 patients) and in no patients undergoing Gamma Knife radiosurgery or staged surgery. However, these analyses were conducted with very few patients and should be interpreted with extreme caution. The authors conclude that these analyses cannot be used to draw conclusions regarding the comparative effectiveness of the treatment strategies.

## Discussion

In terms of the effectiveness results determined *a priori* to be relevant to this review, two studies (one using Gamma Knife radiosurgery alone, the other after surgery) reported no difference in rates of tumour progression between Gamma Knife radiosurgery and surgery (Hart & Giannotta 2003; Linskey, Davis, & Ratanatharathorn 2005). Another larger study reported lower rates of tumour progression for Gamma Knife radiosurgery, and progression-free survival analysis indicated that this was better for those patients undergoing grade 2 resections or higher (Pollock et al 2003). In terms of neurological function, Linskey, Davis, & Ratanatharathorn (2005) found no difference between Gamma Knife radiosurgery and surgery in terms of worsening neurological symptoms; however, the neurological function of Gamma Knife radiosurgery patients was more likely to improve and the functioning of surgical patients was more likely to remain unchanged. Hart and Giannotta (2003) reported no difference in neurological functioning in surgical patients with or without Gamma Knife radiosurgery.

Previous systematic reviews have been unable to draw conclusions regarding the comparative effectiveness of Gamma Knife radiosurgery and alternative treatments. The Level III-2 evidence described above is somewhat inconsistent in the results reported and is of poor methodological quality. All of the studies were retrospective, and each had significant problems with selection bias. Patient characteristics and prognostic factors were reported to differ markedly between treatment arms in both studies using Gamma Knife radiosurgery as a stand-alone treatment, and the comparability of patient groups could not be assessed for the single study using Gamma Knife radiosurgery in addition to surgery. Hence, it is difficult to interpret any observed differences in outcomes between study arms solely to the different treatments. Furthermore, the authors of all three studies note that the follow-up obtained is inadequate to assess the full effects of both treatments, but this applies particularly to Gamma Knife radiosurgery. Therefore, the results from these studies should be regarded as tentative, and longer term follow-up is required before definitive conclusions may be drawn.

The results of Hart and Giannotta (2003) in particular must be interpreted extremely cautiously given the small sample size. It is unlikely that this study is sufficiently powered to detect true differences in effectiveness between the treatments. The analyses of surgical subgroups (single sitting and staged approaches) relied on very few patients, and these groups do not meet the eligibility criterion for this review of at least 10 patients per arm. Similarly, the analysis of atypical or malignant tumours reported by Linskey, Davis, & Ratanatharathorn (2005) does not satisfy this criterion.

No studies were identified which compared Gamma Knife radiosurgery with other forms of SRS (Linac or CyberKnife). Similarly, no studies were identified that compared Gamma Knife radiosurgery with conventional radiotherapy (with or without surgery), or with observation.

Due to the issues described here, the present MSAC review is unable to update the conclusions of the review conducted by Hailey (2002), in which it was stated that no meaningful comparisons may be made between SRS and alternative treatments, or between different types of SRS for the treatment of meningioma.

### **Conclusions**

The methodological quality of the Level III-2 evidence identified by the current review prohibits meaningful conclusions regarding the comparative effectiveness of Gamma Knife radiosurgery (alone or in combination with surgery) and surgery in patients with meningiomas. Similarly, conclusions comparing the effectiveness of Gamma Knife radiosurgery and conventional radiotherapy (with or without surgery), observation, or other forms of SRS (Linac or CyberKnife) are not possible given the lack of comparative studies.

## **Pituitary adenoma**

### **Is it safe?**

#### **Systematic reviews, HTAs and practice guidelines**

Hailey (2002) found evidence for delayed complications from SRS in a study with long-term follow-up. A review by AETMIS (2004) recognises this and notes that further follow-up was required to fully assess safety. However, it is also concluded that complications after SRS are rare, and that SRS seems to be associated with fewer complications than conventional radiotherapy. These conclusions are based at least in part on information not included as part of the systematic review.

#### **Primary studies**

The literature search identified one comparative cohort study investigating the safety of Gamma Knife radiosurgery relative to other comparator treatments (this study is described further in the following section, 'Is it effective?'). No RCTs were found. Case series studies were not considered due to methodological difficulties and inconsistencies in reporting which render comparisons between series of different treatments difficult to interpret.

Ikeda et al (2001) compared patients undergoing surgery for growth hormone (GH) secreting pituitary adenomas with those treated by Gamma Knife radiosurgery in addition to surgery. There was no perioperative mortality, and no patients showed aggravation of pituitary dysfunction either after surgery or Gamma Knife radiosurgery. Visual function (acuity and visual field) remained normal in all patients after Gamma Knife radiosurgery at a mean follow-up of 59 months. The mean follow-up of the surgical group is not reported.

#### **Discussion**

The study by Ikeda et al (2001) is of relatively poor methodological quality, with key elements crucial to interpretation of the results not being reported (the retrospective or prospective nature of patient enrolment, the comparability of patient characteristics between groups, the length of follow-up of surgical patients). Further, the number of

patients undergoing Gamma Knife treatment ( $n = 18$ ) was relatively small, and the sample size overall does not provide sufficient power to investigate differences in safety. In addition, the follow-up period for these patients (approximately five years) is inadequate to assess the long-term safety of Gamma Knife radiosurgery. Although no perioperative mortality or decline in visual or pituitary function was observed in Gamma Knife radiosurgery patients, the systematic review by Hailey (2002) notes the potential for delayed complications. Hence, the utility of this study in terms of assessing safety is limited.

## **Conclusions**

Definitive conclusions about the relative efficacy of Gamma Knife radiosurgery and alternative treatments are not possible. Level III-2 evidence suggests that complications after Gamma Knife radiosurgery in addition to surgery are rare in the short-to-medium term in terms of mortality, pituitary dysfunction or worsening visual function, but long-term safety is uncertain. The methodological limitations of this evidence preclude conclusions about the comparative safety of Gamma Knife radiosurgery and surgery. There were no comparative studies on which to base conclusions on the relative safety of Gamma Knife and conventional radiotherapy (with or without surgery), or different forms of SRS (Gamma Knife, Linac, CyberKnife).

## **Is it effective?**

### **Systematic reviews, HTAs and practice guidelines**

Two systematic reviews of variable quality were identified that addressed the effectiveness of Gamma Knife radiosurgery for pituitary adenomas. Neither review identified RCTs of SRS for pituitary adenomas, and no statistical synthesis of effectiveness data was attempted. Each review provided summaries largely of case series evidence (these studies were ineligible for inclusion in the present MSAC review). Neither of the reviews provided sufficient information to meet all the specified criteria for high-quality reviews; however, Hailey (2002) was considered to be of good quality, and due to an extensive search strategy was unlikely to have missed potentially eligible studies.

Each of the reviews reported results for SRS in general, including both Gamma Knife and Linac-based radiosurgery, and for one review the types of pituitary tumours included in the review were not clear. Table 18 describes the populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

### **Hailey 2002**

This review examined pituitary tumours among other indications. Although of generally good quality, inclusion criteria specific to each indication were not stated, no validation of the application of inclusion criteria or data extraction were undertaken, and the method of quality assessment of included studies was not described. However, since an extensive search was employed, the present MSAC assessment will update the report by Hailey (2002).

**Table 18 Pituitary adenoma: Populations, types of SRS, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews**

Study	Included studies	Patients	Type(s) of SRS	Comparators	Outcomes	Quality
Hailey 2002	15 studies: 1 cohort 14 case series	Pituitary tumours (including adenomas)	GK or Linac	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered tumour control, hormone hypersecretion, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. A single reviewer applied inclusion criteria and extracted data.
AETMIS 2004	6 case series	Pituitary tumours (including adenomas)	GK, Linac, helium ions, proton accelerator	Not defined <i>a priori</i> . Studies compared GK with Linac.	Not defined <i>a priori</i> . Considered tumour control/cure, hormone hypersecretion, complications.	Specific inclusion criteria per indication not provided. Study validity assessed in text, but method of quality assessment unclear. Review methodology not clearly stated.

Abbreviations: AETMIS = Agence d'évaluation des technologies et des modes d'intervention en santé; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

No comparative studies of Gamma Knife radiosurgery and alternative treatments were found. The search identified 12 Gamma Knife radiosurgery case series studies and two case series and one cohort employing Linac-based radiosurgery. The studies primarily examined pituitary adenomas; however, some patients had Cushing's disease or unspecified pituitary tumours. No comparative conclusions were made regarding the efficacy of SRS versus other treatments; however, the included studies indicated good rates of tumour control and normalisation of hormone levels.

#### **AETMIS 2004**

Pituitary tumours were addressed along with other indications for SRS in this HTA report. Quality assessment, inclusion criteria, and methods used to apply these criteria and extract data are not stated.

Two case series addressing Gamma Knife radiosurgery and two case series examining Linac-based radiotherapy were included in the review. One case series each addressing helium ions and proton therapy were also included and contributed to the formation of the conclusions. Specific types of pituitary tumours were not described, but conclusions relate to pituitary adenomas. The authors note that surgery through a transsphenoidal approach is typically opted for over SRS since surgery permits a more rapid correction of hormone hypersecretion, but that Gamma Knife radiosurgery acts faster in reducing hormone hypersecretion than conventional radiotherapy. Gamma Knife radiosurgery was found to be effective in treating pituitary tumours that resist surgical treatment following conventional radiotherapy, and in treating microadenomas and noncompressive sellar tumours when the patient declines surgery or the transsphenoidal approach is not possible. Finally, it is stated that there is no evidence that either Gamma Knife or Linac radiosurgery are superior to one another.

The discussion section of this review referenced many studies that were not included in the systematic review itself, and these additional information sources appear to have contributed to the formation of the conclusions. The degree to which the above conclusions were based on the primary studies systematically identified by the review is unclear, and hence these conclusions must be regarded as tentative.

### **Primary studies**

The systematic literature search was unable to identify any RCTs comparing Gamma Knife radiosurgery with the comparator treatments. Hence, the search was structured to identify non-randomised comparative studies. Two cohort studies were identified, each comparing Gamma Knife radiosurgery in addition to surgery with surgery alone.

#### **Gamma Knife radiosurgery plus surgery versus surgery alone**

In a retrospective cohort study, Picozzi et al (2005) investigated tumour recurrence outcomes in 119 patients with residual non-functioning pituitary adenomas evident on MRI after maximal surgical debulking. A total of 51 patients underwent subsequent Gamma Knife radiosurgery, and the remaining 68 patients did not, either due to patient refusal of Gamma Knife radiosurgery or because conservative management was advised, particularly in older patients with smaller tumours. Despite this apparently selective allocation of treatment strategies, the study arms were balanced on age, gender, number of previous operations, gonadotropinoma, tumour size and follow-up. Patients with follow-up for less than one year were excluded. The mean follow-up was 40.6 months for the surgery plus Gamma Knife radiosurgery group, and 41.6 months for the surgery alone group ( $p = 0.83$ ).

Tumour recurrence in this study was defined as evidence on MRI of pathological tissue not previously detected, or a 20 per cent increase in the volume of the residual tumour. The Gamma Knife radiosurgery group was found to have a significantly lower rate of tumour progression (3.9%) than those patients treated with surgery alone (47.1%) ( $p < 0.001$ ). A five-year progression-free survival rate of 89.8 per cent (95% CI: 76.2–100%) was reported in the surgery plus Gamma Knife radiosurgery treatment arm, compared with 51.1 per cent (95% CI: 37.5–64.8%) in those treated with surgery alone, and this was found to be statistically significant ( $p$ -value not reported).

Ikeda et al (2001) undertook a comparison of Gamma Knife radiosurgery in addition to surgery ( $n = 18$ ) compared with surgery alone ( $n = 72$ ) in a cohort of 90 patients with GH-secreting pituitary adenoma. Gamma Knife treatment was administered more than six months after surgery when there was evidence of persistent GH hypersecretion or tumour regrowth. The study may have been undertaken retrospectively, but this cannot be determined with certainty from information provided in the paper. The comparability of treatment groups was not discussed; however, the gender composition of the groups appeared to be different. The mean age of Gamma Knife radiosurgery patients also appeared to be younger than those undergoing surgery, but this could not be assessed statistically. The mean follow-up for Gamma Knife radiosurgery patients was 59 months; however, mean follow-up for those undergoing surgery alone was not stated. This study assessed biochemical remission after surgery, which was defined as normalisation of the insulin-like growth factor-I level six months after treatment, or a fall in serum GH to below 1 ng/ml following oral administration of 75 g of glucose. Biological remission after Gamma Knife radiosurgery was defined as normalisation of the age-adjusted insulin-like growth factor-I level. In the surgery alone group, 67 per cent of patients achieved biochemical cure, compared with 82 per cent fulfilling biological cure criteria in

those who had additional Gamma Knife radiosurgery ( $p = 0.03$ ). One Gamma Knife radiosurgery patient (6%) was lost to follow-up.

## Discussion

One study addressing each of the outcomes of tumour progression and hormone function (specified *a priori* as relevant to the present review) were identified. Picozzi et al (2005) reported a significantly lower rate of recurrence in patients receiving Gamma Knife radiosurgery than those undergoing observation in a sample with residual non-functioning pituitary adenoma after surgical debulking. Interpretation of these results is problematic because at least some of the patients not receiving Gamma Knife radiosurgery would typically undergo some form of radiation therapy to limit the possibility of recurrence because it is known that patients with incomplete resection are more likely to have progression of the tumour. Hence, a more appropriate comparator for Gamma Knife radiosurgery in this patient group would be surgery plus conventional radiotherapy rather than observation. However, this study does seem to confirm that patients undergoing Gamma Knife radiosurgery for residual tumour after surgery experience better outcomes in terms of progression than those who undergo surgery, then observation.

In terms of hormone function, Ikeda et al (2001) found higher rates of biological cure in patients with GH-secreting adenomas treated with a combination of surgery and Gamma Knife radiosurgery than rates of biochemical cure in patients only undergoing surgery. Different definitions of cure were applied to the treatment arms, and combined with the inability to assess baseline patient differences between groups, the lack of information about post-surgical follow-up, and the uncertainty regarding whether this was a retrospectively identified cohort, it is difficult to draw conclusions from this study.

It should be noted that these studies consider only two types of pituitary adenoma. The outcomes of treatment are known to differ markedly by the type of tumour, and hence it would be unwise to generalise any conclusions based on these two studies to the broad group of patients with pituitary adenomas as a whole.

There were no studies considering cognitive function, an additional outcome specified *a priori* as relevant to this review. In terms of the other comparators of interest, no studies were identified comparing Gamma Knife radiosurgery with radiotherapy (alone or in combination with surgery) or with observation alone. Similarly, no studies compared Gamma Knife radiosurgery with either Linac or CyberKnife.

## Conclusions

There is Level III-2 evidence that patients with residual non-functioning pituitary adenoma after surgery benefit from Gamma Knife radiosurgery in terms of tumour progression, compared with patients who are observed after surgery. However, there is no evidence comparing the rates of tumour progression in such patients undergoing radiotherapy after surgery. The methodological quality of the evidence does not permit conclusions regarding the relative effectiveness of Gamma Knife radiosurgery in terms of post-treatment hormone function. No comparisons between Gamma Knife radiosurgery and radiotherapy (either alone or in combination with surgery) or observation alone are possible. Similarly, this review is unable to address comparisons on effectiveness between Gamma Knife and other forms of SRS (Linac and CyberKnife).

## What are the economic considerations?

Economic evaluation in HTA attempts to assess potential health benefits and costs of a new therapy. Frequently a new technology is both more costly and more effective than the comparator. Clearly there will always be a limit to the additional costs (incremental costs) paid for any health gain (incremental effect) due to limited health care resources. Economic evaluation attempts to measure the trade-off between incremental costs and effects using cost-effectiveness analysis; expressed most frequently in terms of the incremental cost-effectiveness ratio (ICER).

ICER = incremental costs/incremental effect.

The ICER represents the dollar cost per health gain (that is, cost per life year saved) of the new treatment versus a comparator treatment. This dollar value can be compared to the amount decision makers are willing to pay for a health gain to help assess whether limited resources should be invested in that technology.

This report has sought to compare Gamma Knife radiosurgery against alternative SRS treatment methods (Linac and CyberKnife), as well as evaluate Gamma Knife radiosurgery in the context of the broader range of available therapies used to treat patients with intracranial lesions (surgery and EBRT). The economic evaluation focuses on the direct comparison between Gamma Knife and other SRS comparators (Linac and CyberKnife).

In order to conduct a full economic evaluation of Gamma Knife versus Linac and CyberKnife radiosurgery, comparative evidence on both the costs and effects of each therapy are required. Unfortunately this report has revealed a lack of substantive evidence about the comparative effectiveness and safety of Gamma Knife radiosurgery. It is not possible to conclude from the available published data whether Gamma Knife radiosurgery is equivalent to or better than other forms of SRS. As a result, a formal economic evaluation can not be conducted and the purpose of this economic evaluation is to provide an update of the previous basic economic costing. This partial evaluation is not a cost minimisation analysis, in which the least costly strategy would indicate the preferred choice. That would be performed if equivalence in effect had been demonstrated (no difference in health gains between strategies). Lack of evidence on effect is not the same as establishing equivalence in effect. Data limitations essentially mean little inference can be drawn from the results of the cost analysis below; the least costly strategy may not necessarily be the preferred choice.

### Findings of the 2001 MSAC report

The previous MSAC report (2001) compared the direct costs of Gamma Knife and Linac radiosurgery. Estimates of the equipment cost per treatment over a range of scenarios showed that Gamma Knife radiosurgery was consistently 1.7 to 2.9 times more expensive than Linac-based treatment. These estimates varied depending on estimates of the upfront capital acquisition costs of the equipment, the useful life of the equipment and the number of treatments performed per year. The costing analysis did not take into account the costs of follow-up for each intervention, in particular, for adverse events.

The report identified important gaps in Australian data that are available to determine the costs of the equipment and associated medical care associated with the different services. The report also provided a summary of five descriptive or partial economic evaluations published up to 1999. Two studies compared Gamma Knife radiosurgery with surgery for the treatment of unspecified indications (Ott 1996) or acoustic neuroma (van Roijen et al 1997). Two studies compared Gamma Knife with Linac radiosurgery for unspecified indications (Becker, Kortmann, & Bamberg 1998; Konigsmaier et al 1998). The fifth study evaluated Gamma Knife radiosurgery and whole brain radiotherapy versus surgery and whole brain radiotherapy for the treatment of solitary cerebral metastases (Rutigliano et al 1995). All five studies were conducted in North America or Europe, which limited the applicability of the results to the Australian health system because of major differences in patterns of health resource utilisation and unit costs between countries.

## Existing literature

The literature search described in the 'Approach to Assessment' section of this report identified one paper that included a formal economic evaluation of Gamma Knife radiosurgery to treat intracerebral lesions (Wellis et al 2003). Two of the four health technology assessment reports identified included a comparative assessment of the costs of stereotactic radiosurgery (Hailey 2002; AETMIS 2004), and one HTA agency published a modelled costing comparing Gamma Knife with Linac radiosurgery (Ohinmaa 2003). The report by Hailey (2002) did not identify any additional evidence to update the previous MSAC report (2001) and is not discussed further.

An additional literature search was conducted to identify economic evaluations of Gamma Knife radiosurgery published since the previous MSAC report (search date: 1999 to July 2005). This search strategy combined the MeSH terms used to define Gamma Knife radiotherapy with terms containing 'cost' or 'econ'. Databases searched were: Medline, Pre-Medline, Embase and Current Contents.

A total of 143 economic papers were identified. Of these, six papers were retrieved for appraisal. One of these papers reported on an economic evaluation of Gamma Knife radiosurgery. This study was also identified in the primary literature search (Wellis et al 2003).

The results of these three studies are summarised in Table 19.

**Table 19 Costing and economic analyses of Gamma Knife radiosurgery published since 1999<sup>a</sup>**

HTA reports				
Reference	Methods		Results	
Hassen-Khogja et al 2004	Assessment of: Capital and annual operating costs Per-patient treatment costs Based on literature review of: Cost comparisons GK versus Linac services (5 studies) SRS versus surgery (3 studies) Cost-effectiveness analyses GK versus surgery for solitary brain metastases (1 study) Some of these studies were also reviewed in the previous MSAC report (2000)		<b>Capital and annual operating costs</b> GK purchase and renovation costs higher than a dedicated Linac, but GK operating costs lower than those for a dedicated Linac. Overall GK estimated to be more costly than modified Linac (but offers greater patient capacity) and less costly than dedicated Linac <b>Per-patient cost of treatment</b> Based on assumed lifespan of 20 years for GK and 10 years for Linac GK more costly than dedicated or modified Linac for patient loads ≤150 per year GK less costly than dedicated Linac for patient loads ≥250 per year. If use of modified Linac facilities is shared between radiotherapy and SRS services then patient loads >150 may not be achieved and the high load GK cost per-patient compares favourably with the cost per patient using modified Linac at a lower load. The number of eligible cases that are treated is critical to this assessment. <b>Barriers to cost-effectiveness analysis reported:</b> Lack of evidence to assess relative effectiveness of GK versus Linac Treatment costs vary according to patients clinical status and selection of first-line treatment	
Individual studies				
Reference	Setting	Objective and study design	Methods	Results and appraisal
Ohinmaa 2003	Canada	Cost comparison of GK, CK and Linac Indications: head/neck lesions	<b>Cost analysis</b> -Hypothetical cost model Direct medical costs = equipment, construction of facility, staff salaries, supplies, equipment maintenance. Assumed to be fixed for each procedure. (Diagnostic work-up and patient follow-up assumed to be equivalent for each procedure and not assessed). Patient-borne costs = hotel costs associated with patient visit, lost working time, caregiver costs.	GK marginally less costly than Linac and less costly than CK. <b>Average per-patient treatment cost</b> GK \$14,567 Linac \$14,889 CK \$16,690 These cost estimates are based on the following assumptions: —treatments are equally effective —interest rate = 0% —patient load = 100 per year

Individual studies				
Reference	Setting	Objective and study design	Methods	Results and appraisal
Wellis et al 2003	Germany 1998-1999	Cost comparison of GK versus surgery Indications: intracerebral lesions amenable to GK and surgery	Cost analysis Direct costing GK costs included: Depreciation, personnel, planning studies, operating costs, taxes, investment debts. Total costs over one year were divided by number of treatments over one year (284). Complications not reliably identified. Surgery costs included: surgical procedure, intensive care unit care, medical and nursing ward care, hospital overheads, follow-up clinical services. Patient population: AVM (17%), acoustic neuroma (19%), meningioma (54%), cerebral metastases (10%). Excluded lesions >3cm or lesions near optic nerve or tract	GK less costly than surgery for patients amenable to both treatments. GK: average cost per patient treatment €7.920 Surgical group: average primary treatment cost per patient €10.814+/-6.108 based on average hospital stay 15.4 +/-8.6 days; ICU 1.2 +/-2.8 days; and total operating theatre time 393+/-118 minutes. Average total treatment cost per patient €15.242 includes ancillary care after neurosurgical treatment such as radiotherapy and rehabilitation (required by 70% of patients) and unplanned readmissions for management of complications (20%). These cost estimates are based on the following assumptions: —treatments are equally effective —follow-up costs after GK are negligible The relative costs will vary according to the number of patients treated with GK over a one-year period.

Abbreviations: AVM = arteriovenous malformation; CK = CyberKnife radiosurgery; GK = Gamma Knife radiosurgery; Linac = linear accelerator radiosurgery; MSAC = Medical Services Advisory Committee; SRS = stereotactic radiosurgery.  
a The literature review published by Hailey (2002) did not identify any studies to update the previous MSAC report (2000) and is not included in this table

## Interpretation

### Gamma Knife radiosurgery versus surgery

The findings of Wellis et al (2003) in favour of Gamma Knife radiosurgery versus surgery are consistent with the results of the three earlier studies reviewed in the previous MSAC report (Ott 1996; van Rooijen et al 1997; Rutigliano et al 1995).

### Gamma Knife versus Linac radiosurgery

The costing presented by Ohinmaa (2003) suggests that Gamma Knife is less costly than Linac radiosurgery (assuming equal effectiveness) at a patient load of 100 patients per year. This finding differs from the results of two studies reviewed in the previous MSAC report (2001) and the more recent Canadian costing based on one of these studies (Hassen-Khogja et al 2004) that have suggested that Gamma Knife radiosurgery is more costly than both modified Linac and dedicated Linac radiosurgery at patient loads of less than 200 patients per year.

Unfortunately, economic analyses conducted outside Australia cannot be applied directly to the Australian health system because of major differences in patterns of health resource utilisation and unit costs between countries. Managed care arrangements, such as those in the United States, also preclude any direct application of costing information. It is relevant, however, that these evaluations indicate that the number of radiosurgery

treatments per year is a critical variable for determining the relative cost of treatment options.

## Cost Analysis

### Major capital equipment

The cost analysis compares Gamma Knife radiosurgery with dedicated Linac and CyberKnife cranial only SRS systems. Unlike Gamma Knife radiosurgery, both Linac and CyberKnife can also be purchased with whole body and fractionated SRS treatment options. The dedicated cranial SRS systems are, however, the closest Gamma Knife radiosurgery comparators and hence have been costed for the purposes of this analysis.

Cost estimates have also been provided for adding SRS capability to an existing Linac radiotherapy system (micro multileaf collimator and stereotactic hardware and software). Two estimates have been provided. The first considers purely the cost of the adaptation unit (excludes the purchase of the Linac system to be adapted). A second analysis considers the cost of both the adaptation equipment and the Linac system itself. Clearly, in reality a proportion of the Linac system capital costs would be allocated to SRS treatment costs (rather than all or nothing). The proportion of costs attributed would vary according to the amount of time equipment was used for SRS and 'other' patient treatment.

An adapted Linac system is not identical to Gamma Knife; the adapted unit has additional flexibility to treat non-SRS patients. Capital equipment and associated staff resources could therefore be used to treat patients with other disorders during SRS treatment downtime (assuming equipment was not utilised to full capacity servicing SRS patient requirements).

System manufacturers or their appropriate Australian representatives were asked to provide standard list cost estimates (2005) for the purchase and maintenance of each of the three SRS comparators. The costs presented in Table 20 have been based on manufacturer estimations with panel member review. While it is recognised that this approach has drawbacks, limited published Australian cost data and the lack of existing CyberKnife or Gamma Knife facilities in Australia inhibited alternative cost analyses.

The cost of a standard Linac system was estimated as A\$1.9 million to A\$2.4 million, depending on system options. A conservative (higher) estimate of \$2.4mn AUD was therefore considered in cost estimates for the Linac adaptation equipment and varied in subsequent sensitivity analyses.

Cost estimates provided included delivery and basic installation but excluded room modifications (for instance, shielded bunker works).

### Maintenance and warranty costs

Both Gamma Knife and Linac representatives provided cost information for an ongoing annual service contract which included maintenance, technical support, training and software upgrades.

Gamma Knife advanced service contract was quoted as US\$115,000 per annum (A\$157,500, based on an exchange rate of 0.73; see Table 20). A comprehensive service contract for Linac was included in the purchase price for the first year (one-year warranty

for all Linac systems) and then estimated as 7 to 8 per cent per annum. Panel members indicated that a higher maintenance charge (for example, 10%) was generally budgeted for by hospitals. The base case analysis has used the higher manufacturer estimate (8%) for both the dedicated and adapted systems, with the 10 per cent estimation used in sensitivity analyses.

The service contract for CyberKnife was estimated by the representative to be US\$350,000 per annum (A\$480,000).

### **Cost of facility works**

All SRS systems include installation in the upfront purchase costs. However, additional facility works required for system operation (for instance, bunker shielding) were not incorporated. Spare bunkers may be available in some cases; however, bunker construction would be necessary in others and this would come at a significant extra cost. The advisory panel indicated that the cost of facility works is highly variable depending on location, and hence it is not appropriate to include it in the cost analysis. No estimation of these costs is therefore included, although it appears that CyberKnife systems require greater shielding (additional floor and ceiling shielding) than standard Linac systems.

### **Quality assurance and radiation test requirements**

Quality Assurance (QA) requirements vary for each technology.

The Gamma Knife representative indicated that a positional accuracy check which takes approximately two to three minutes was required every morning (software included in purchase) and one radiation dose check per year (included in the advanced service contract).

The Linac and CyberKnife systems require a radiation dose check (Winston Lutz test) to ensure that the radiation dose is delivered exactly to the centre of the planned target. This is done every morning before the treatment day commences and takes approximately 20 minutes. The equipment required to conduct this test is also included in the purchase price.

### **Other additional costs**

All system representatives reported that, with routine maintenance and service, refurbishment should not be required during the estimated useful working life of the equipment. Refurbishments costs were therefore not included into the cost analysis. Service contracts included call-out, labour and faulty parts. Wear of parts would be an additional expense and would vary according to the component.

Previous economic costings (Ohinmaa 2003) have indicated that the utilisation of basic supplies and nursing support are similar. Panel members also agreed these costs would not be substantially different. Analysis on basic supplies has not therefore been undertaken.

Staffing costs have also not been considered, although previous reviews have indicated there may be lower staffing requirements for a Gamma Knife system (Ohinmaa 2003).

### Useful working life

Gamma Knife equipment is generally expected to have a longer useful working life than CyberKnife or Linac systems due to fewer moving parts. Manufacturer estimations for working life were 15, 12, and 10 years for Gamma Knife, CyberKnife and Linac systems, respectively. The previous 2001 MSAC report indicated some facilities operated Linac machines beyond a 10-year term (for instance, up to 13 years). However, Australian hospitals generally budget for a minimum of a 10-year working life. The base case cost analysis therefore uses the manufacturers estimates of 15 years for Gamma Knife, 10 years for Linac and 12 years for CyberKnife systems.

### Cobalt source reload

Gamma Knife is the only SRS comparator to require a cobalt source reload. The manufacturer estimated that this would be required every six to seven years at a cost of US\$750,000 (A\$1,027,397; exchange rate 0.73) with an associated downtime of two to three weeks (see Table 20). This cost estimate included disposal of the old source. The base case analysis assumed two reloads would be required, using a 15 year life expectancy for Gamma Knife. Reloads have been modelled to occur at the end of years 5 and 10 (beginning of years 6 and 11). This is slightly sooner than the manufacturer estimate; however, it is understood that treatment times increase as the cobalt source ages and therefore it is preferable to replace the cobalt source after five years rather than after seven years (Smee 2000). Costs associated with equipment downtime resulting from the reload have not been included.

**Table 20 Estimated costs of Gamma Knife and SRS comparators**

	Gamma Knife	CyberKnife	Linac Dedicated SRS system	Linac Adaptation Equipment (Linac unit excluded from costs)	Linac Adaptation Equipment (Linac system included in costs)
Equipment purchase cost	\$5,301,370	\$5,064,384	\$3,698,630	\$890,411	\$3,290,411
Service contract <sup>a</sup>	\$157,534	\$479,452	\$295,890	\$71,233	\$263,233
Radiation source reload (and disposal of old source)	\$1,027,397	–	–	–	–
Manufacturers estimated useful life, years	15	12	10	10	10

Abbreviations: Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.  
Interest rate 5 per cent.

All figures presented are all quoted in Australian dollars and have been converted from US dollars using the most recently published Organisation for Economic Co-operation and Development purchase parity rate (2004) of 0.73 US\$/A\$.

<sup>a</sup> a Linac service contract cost estimated as 8 per cent of equipment purchase cost.

## Cost analysis

Capital equipment purchase cost and maintenance estimates from Table 20 have been distributed over the expected life time of the systems in order to calculate an expected annual capital equipment cost for each comparator (see Table 21). Cost estimations are presented for a range of equipment life expectancies. A discount factor of 5% per cent has been applied in line with current Australian recommendations (Commonwealth Department of Health and Ageing 2002).

**Table 21 Cost analysis**

Discounting year	Gamma Knife	CyberKnife	Linac dedicated SRS system	Linac adaptation equipment (Linac unit excluded from costs)	Linac adaptation equipment (Linac unit included in costs)
0	\$5,458,904	\$5,543,836	\$3,994,521	\$890,411	\$3,290,411
1	\$150,033	\$456,621	\$281,800	\$67,841	\$250,698
2	\$142,888	\$434,877	\$268,381	\$64,610	\$238,760
3	\$136,084	\$414,169	\$255,601	\$61,534	\$227,390
4	\$129,604	\$394,446	\$243,430	\$58,603	\$216,562
5	\$928,425	\$375,663	\$231,838	\$55,813	\$206,250
6	\$117,554	\$357,775	\$220,798	\$53,155	\$196,428
7	\$111,957	\$340,738	\$210,284	\$50,624	\$187,075
8	\$106,625	\$324,512	\$200,270	\$48,213	\$178,166
9	\$101,548	\$309,059	\$190,734	\$45,917	\$169,682
10	\$727,445	\$294,342	\$181,651	\$43,731	\$161,602
11	\$92,107	\$280,326	\$173,001	\$41,648	\$153,907
12	\$87,721	\$266,977	\$164,763	\$39,665	\$146,578
13	\$83,544	\$254,264	\$156,917	\$37,776	\$139,598
14	\$79,565	\$242,156	\$149,445	\$35,977	\$132,950
Average SRS capital equipment cost by life expectancy					
10 years <sup>a</sup>	\$748,033	\$924,604	\$627,931	\$144,045	\$532,303
11 years	\$688,404	\$866,033	\$586,574	\$134,736	\$497,903
12 years	\$638,347	\$816,112	\$551,423	\$126,814	\$468,626
13 years	\$644,188	\$772,893	\$521,076	\$119,965	\$443,316
14 years	\$603,857	\$734,983	\$494,531	\$113,966	\$421,147
15 years	\$563,600	\$685,984	\$461,562	\$106,368	\$393,071

Abbreviations: Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

Assumptions:

Service contract costs are assumed to occur at beginning of each year.

Gamma knife cobalt source replacement assumed to occur at end of years 5 and 10 (beginning of year 6 and 11 respectively).

<sup>a</sup> Cost of 10-year cobalt reload excluded for 10- and 11-year Gamma Knife life expectancy.

## Average capital cost per annum

The base case analysis assumes a 10- year life expectancy for all Linac systems, 12 for Cyber knife and 15 for Gamma Knife (see Table 22).

**Table 22 Base Case average capital cost per annum**

Least costly system	Gamma Knife	CyberKnife	Linac dedicated SRS system	Linac adaptation equipment (Linac unit excluded from costs)	Linac adaptation equipment (Linac unit included in costs)
Linac adaptation equipment	\$563,600	\$816,112	\$627,931	\$144,045	\$532,303

Abbreviations: Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

Assumptions:

Life expectancy 10 years Linac, 12 years CyberKnife, 15 years Gamma knife.

Cobalt reload end of begin year 6 & 11.

Discount rate 5 per cent.

Purchase/service costs incurred at beginning of each year.

## Cost per patient

The average cost of capital per patient has been calculated using estimations of likely patient volumes for an SRS facility.

Recent Australian estimates of Linac radiosurgery usage are tabulated in Table 23.

**Table 23 Estimates of Linac radiosurgery usage**

Source		
Requested Medicare items processed from July 2003 to June 2004	Item 15600 Stereotactic radiosurgery	154 (Number of treatment episodes nationally)
2004 NSW Radiotherapy management information system report	Stereotactic radiosurgery, single dose patient number	97 (Number of patients NSW)
2004 NSW Radiotherapy management information system report	Stereotactic radiosurgery, fractionated patient number	76 (Number of patients NSW)

Data about the current utilization of stereotactic radiosurgery in Australia is limited (as shown in Table 23). The MBS estimate only represents services rebated through Medicare (that is, private patient admissions and outpatient services). It is clear that the majority of hospital (public provisioned) services would be excluded from these figures and therefore it underestimates the volume of stereotactic radiosurgery services currently carried out. The NSW radiotherapy report indicates that approximately 173 patients were treated in two hospitals in NSW (NSW Health 2005). The vast majority (165) of these were carried out at the Prince of Wales Hospital due to the alternative facility being under repair during that period. The base case cost per patient has therefore been estimated using a patient volume of 150 patients.

The cost per patient for Gamma Knife, CyberKnife, dedicated Linac and adapted Linac was \$3,757, \$5,441, \$4,186 and \$3,549 respectively. It is recognised that these are crude

estimates, as patient volumes particularly are likely to vary substantially between facilities. Estimates of plausible costs per patient based on alternative patient numbers (50, 100, 200 and 400 patients per annum) have been provided in Table 24. A number of overseas economic analyses, although not directly applicable to Australia, have suggested that a Gamma Knife facility is more costly to run than a modified Linac facility at small radiosurgery patient volumes (that is, 200 or less).

**Table 24 Base case average capital equipment costs per patient**

	Gamma Knife	CyberKnife	Linac dedicated SRS system	Linac adaptation equipment (Linac unit excluded from costs)	Linac adaptation equipment (Linac unit included in costs)
Equipment life expectancy	15	12	10	10	10
Patients per Annum					
50	\$11,272	\$16,322	\$12,559	\$2,881	\$10,646
100	\$5,636	\$8,161	\$6,279	\$1,440	\$5,323
150	\$3,757	\$5,441	\$4,186	\$960	\$3,549
200	\$2,818	\$4,081	\$3,140	\$720	\$2,662
400	\$1,409	\$2,040	\$1,570	\$360	\$1,331

Abbreviations: Linac = linear accelerator radiosurgery; SRS = stereotactic radiosurgery.

**Table 25 Base case incremental cost per patient for Gamma Knife versus adapted Linac**

Sensitivity analyses	Incremental cost per patient (based on 150 patients per annum) gamma knife versus adapted Linac	
	Linac Adaptation Equipment (Linac unit \$2.4 million excluded from costs)	Linac Adaptation Equipment (Linac unit \$2.4 million included in costs)
Base case	\$2,797	\$209

Abbreviations: Linac = linear accelerator radiosurgery.

## Results

The base case analysis (see Tables 22 and 24) indicates that an adapted Linac system would offer the least costly method of providing SRS treatment in Australia regardless of whether capital acquisition costs associated with a standard Linac system (estimated at A\$2.4 million) were taken into consideration. The base case estimate for the cost per patient for an adapted unit ranged between \$960 (when the Linac unit, at A\$2.4 million, is excluded from the cost) and \$3,549 (when the Linac unit, at A\$2.4 million, is included in the cost). The cost per patient is estimated to be \$3,757 using Gamma Knife equipment. The incremental cost per patient for Gamma Knife versus adapted Linac equipment for 150 patients per year was therefore an additional \$209 to \$2,797 (Table 25). For an annual patient volume of 50 patients, the estimate for the cost per patient for an adapted Linac unit ranged between \$2,881 (when the Linac unit, at A\$2.4 million, is excluded from the cost) and \$10,646 (when the Linac unit, at A\$2.4 million, is included

in the cost). The estimate for the cost per patient for Gamma Knife equipment is \$11,272. The incremental cost per patient for Gamma Knife versus an adapted Linac for 50 patients per year was therefore an additional \$626 to \$8,391.

If only the dedicated systems were taken into consideration (excluding the adapted Linac system), Gamma Knife was estimated to be the least costly of the three options reviewed, with an incremental cost per patient of -\$429 versus the Linac dedicated system and -\$1,683 versus CyberKnife (150 patients per year).

### **Sensitivity analyses**

One-way sensitivity analyses performed on the base case indicate results are potentially sensitive to variations in assumptions (see Table 26).

In the base case analysis, the Linac unit used with adaptation equipment was assumed to cost A\$2.4 million (the higher Department of Health cost estimate). If that cost were entirely attributed to SRS treatment costs, in other words the adapted Linac was used only for SRS treatment, Gamma Knife may offer a lower cost per patient when base assumptions on the number of cobalt reloads and the Linac maintenance charges are varied. If one Gamma Knife cobalt reload (rather than two) were required, or if Linac maintenance charges were actually 10 per cent of the purchase price (rather than 8 per cent) Gamma Knife was estimated to offer an incremental cost per patient (-\$105 and -\$130, respectively). Obviously the best case Gamma Knife scenario occurs if both of these assumptions apply; assuming 150 patients per year in the considered case, Gamma Knife equipment may be as much as \$444 per patient less expensive than an adapted Linac unit.

However, if a base Linac unit costs A\$1.9 million (the lower Department of Health estimate), Gamma Knife has a higher cost per patient than an adapted Linac regardless if one cobalt reload is assumed or higher Linac maintenance charges (10%) are applied. Using this cost and applying all other base case assumptions (two reloads and 8% maintenance charge), Gamma Knife may be as much as \$748 to \$2,797 per patient more expensive than an adapted Linac unit.

Other sensitivity analyses performed on equipment working life indicate that base case results are compounded if all systems are modelled to have the same working life (12 years). Under these assumptions Gamma Knife was between \$1,131 and \$3,410 per patient more expensive than an adapted Linac. In a worse case Gamma Knife scenario (low capital cost and same working life), the incremental cost per patient for Gamma Knife versus an adapted Linac system was shown to be \$1,606 to \$3,410.

In all considered scenarios the estimated cost per patient for Gamma Knife equipment was lower than the alternative CyberKnife and Linac dedicated systems.

Varying the applied discount rate to 0 and 8 per cent did not alter the order of base case results. The adapted Linac system offered the lowest cost per patient, followed by Gamma Knife, Linac dedicated system and CyberKnife in both scenarios.

**Table 26 Sensitivity analyses**

Sensitivity analyses	Average annual capital cost <sup>a</sup>			Incremental cost per patient (based on 150 patients per annum) Gamma Knife versus adapted Linac	
	Gamma Knife	Linac adaptation equipment (Linac unit excluded from costs)	Linac adaptation equipment (Linac unit \$2.4 million included in costs)	Linac Adaptation Equipment (Linac unit excluded from costs)	Linac Adaptation Equipment (Linac unit \$2.4 million included in costs)
Base case	\$563,600	\$144,045	\$532,303	\$2,797	\$209
1 cobalt reload (end of year 7)	\$516,562	\$144,045	\$532,303	\$2,483	-\$105
10% per annum Linac maintenance costs	\$563,600	\$157,796	\$583,118	\$2,705	-\$130
Working life 12 years all systems	\$638,347	\$126,814	\$468,626	\$3,410	\$1,131
Base Linac unit capital cost A\$1.9 million	\$563,600	\$144,045	\$451,416	\$2,797	\$748
Base Linac unit capital cost A\$1.9 million and working life 12 years and working life 12 years (worst case Gamma Knife)	\$638,347	\$126,814	\$397,415	\$3,410	\$1,606
1 cobalt reload and high Linac maintenance costs (Best case Gamma Knife)	\$516,562	\$157,796	\$583,118	\$2,392	-\$444

Abbreviation: Linac = linear accelerator.  
<sup>a</sup> Costs given in Australian dollars.

## Conclusions

Estimates of equipment cost per patient depend on the upfront capital acquisition costs, the useful life of the equipment, annual maintenance costs and SRS patient volumes per year.

The base case cost analysis indicates that an adapted Linac would provide the least costly method of SRS treatment in Australia

Assuming a high base Linac unit cost (\$2.4 million) and assuming an adapted Linac would be dedicated only to SRS treatment, the results of this analysis have been shown to be sensitive to variations in the number of cobalt reloads and the costs of Linac maintenance. The Gamma Knife unit potentially offers a lower cost per patient than an adapted Linac if only one cobalt reload (rather than two) is required during its useful working life, or if annual Linac maintenance charges are actually 10 per cent of the purchase price (rather than 8%).

However, a cost of \$2.4 million for a base Linac unit (used in conjunction with the adaptation equipment) is a conservative assumption which favours the Gamma Knife system. If an adapted Linac system were used only for SRS purposes, then a base Linac unit with the minimum add-on options may be chosen (potentially resulting in the lower purchase cost).

Sensitivity analyses using the lower Department of Health cost estimate of \$1.9 million for the base Linac unit result in a higher incremental cost per patient for Gamma Knife versus an adapted Linac unit regardless of assumptions about cobalt reloads and Linac maintenance charges.

In addition, if an adapted Linac were used for other therapies, only a proportion of the capital costs associated with the base Linac unit would be attributed to SRS treatment costs. The relevant proportion would depend on the percentage of equipment working time spent on SRS versus any alternative therapy. The base Linac capital costs attributed to SRS would therefore be lower than the base case estimate of \$2.4 million. Sensitivity analyses show that once these costs fall below \$2 million a Gamma Knife unit has a higher incremental cost per patient than an adapted Linac unit, even in a best case Gamma Knife scenario.

This costing is not a cost minimisation analysis and the least costly option may not be the preferred choice. The effectiveness of Gamma Knife versus alternatives such as adapted Linac systems needs to be better established so that a full cost-effectiveness analysis can be performed and greater inference can be drawn from results.

# Conclusions

---

## Safety

### Cerebral metastases

There is Level II evidence which suggests that the addition of SRS to WBRT results in a slightly increased risk of serious radiation-related toxicity compared with WBRT alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. The present review is unable to update the conclusions of the previous MSAC assessment in terms of the relative safety of Gamma Knife and Linac radiosurgery, and there were no studies on which to base conclusions regarding the comparative safety of Gamma Knife and CyberKnife radiosurgery. The comparative safety of these different types of SRS remains uncertain. Similarly, no conclusions are possible regarding the comparative safety of Gamma Knife radiosurgery and surgery plus WBRT.

### Arteriovenous malformations

In the absence of additional comparative evidence since the completion of MSAC's previous assessment of Gamma Knife radiosurgery, this review is unable to update those conclusions. Event rates appear to be similar in patients treated with Gamma Knife and Linac radiosurgery, but methodological limitations, patient selection biases and inconsistencies in the reporting of adverse events prevented meaningful comparisons between the safety of Gamma Knife and Linac radiosurgery, and surgery.

### Acoustic neuroma

There is Level III-2 and III-3 evidence that Gamma Knife radiosurgery appears to result in a lower rate of medium-term treatment-related complications and procedural mortality than does surgery. However, methodological limitations of these studies preclude conclusions regarding the magnitude of that effect. The relative long-term safety of Gamma Knife radiosurgery and surgery could not be assessed. There was no evidence on which to base a comparison between Gamma Knife and other forms of SRS (Linac and CyberKnife).

### Primary malignant lesions

There is Level II evidence that the addition of SRS to conventional radiotherapy plus chemotherapy (BCNU) results in a slightly increased risk of late grade 3 radiation-related toxicity compared with EBRT and BCNU alone. It is uncertain how this finding applies to Gamma Knife radiosurgery specifically. No conclusions about the relative safety of Gamma Knife and alternative forms of SRS (Linac and CyberKnife) are possible.

## **Meningioma**

Due to methodological limitations of the included Level III-2 studies, it is not possible to draw definitive conclusion regarding the relative safety of Gamma Knife radiosurgery and surgery. Complications after Gamma Knife radiosurgery tend to be transitory in the short-to-medium term, but inadequate follow-up precludes conclusions about long-term safety. A lack of comparative evidence further precludes conclusions regarding the relative safety of Gamma Knife and conventional radiotherapy (alone or in combination with surgery), and other forms of SRS (Linac and CyberKnife).

## **Pituitary adenoma**

Definitive conclusions about the relative efficacy of Gamma Knife radiosurgery and alternative treatments are not possible. Level III-2 evidence suggests that complications after Gamma Knife radiosurgery in addition to surgery are rare in the short-to-medium term in terms of mortality, pituitary dysfunction or worsening visual function, but long-term safety is uncertain. The methodological limitations of this evidence preclude conclusions about the comparative safety of Gamma Knife radiosurgery and surgery. There were no comparative studies on which to base conclusions on the relative safety of Gamma Knife and conventional radiotherapy (with or without surgery), or different forms of SRS (Gamma Knife, Linac, CyberKnife).

## **Effectiveness**

### **Cerebral metastases**

There is Level II evidence that the addition of SRS to WBRT does not improve or decrease overall survival compared to WBRT alone in patients with multiple cerebral metastases. However, there is Level II evidence of a small but statistically significant improvement in survival (1.6 months) when SRS is used as a boost to WBRT in patients with single metastases. SRS may lead to improvements in tumour control and patient performance in patients with up to three metastases; however, definitive conclusions are not possible.

There is Level III-2 evidence that there is no difference in overall survival between patients with multiple cerebral metastases treated by Gamma Knife versus Linac-based radiosurgery (in addition to WBRT).

There were no studies on which to base conclusions regarding the relative effectiveness of Gamma Knife and CyberKnife radiosurgery. Similarly, no conclusions are possible concerning a comparison between Gamma Knife radiosurgery and observation.

### **Arteriovenous malformations**

In the absence of comparative studies, this assessment is unable to update the findings of the previous MSAC review and the systematic review conducted by Hailey (2002). Gamma Knife radiosurgery should continue to be regarded as a complimentary approach to surgery in patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention. There is no evidence on which to base conclusions

about the relative effectiveness of Gamma Knife, Linac and CyberKnife radiosurgery for the treatment of AVM.

### **Acoustic neuroma**

Due to the methodological quality of the Level III-2 and Level III-3 evidence identified by the current review, it remains difficult to draw firm conclusions regarding the relative effectiveness of Gamma Knife radiosurgery compared with surgery to treat acoustic neuroma. It is not possible to advance the conclusions reported in the previous MSAC assessment. Gamma Knife radiosurgery appears to offer similar outcomes in terms of tumour control to those from surgery. Gamma Knife radiosurgery may offer some benefits in terms of quality of life, hearing preservation and facial function in selected patient groups for whom surgery is not indicated, but in the absence of randomised controlled studies there is considerable uncertainty in specifying the magnitude of benefit. No comparison between Gamma Knife and Linac-based radiosurgery was possible, and hence the tentative conclusion reported in the previous MSAC review of little difference between the modalities is still applicable. Further, there were no studies on which to base conclusions on the comparative effectiveness of Gamma Knife and CyberKnife radiosurgery.

### **Primary malignant lesions**

There is Level II evidence that the addition of SRS to EBRT, surgery and chemotherapy does not improve or decrease survival, neurological function or quality of life compared with EBRT, surgery and chemotherapy alone in patients with primary malignant lesions (glioblastoma multiforme). There is Level III-2 evidence that there is no difference in overall survival between patients treated by Gamma Knife versus Linac-based radiosurgery (in addition to surgery, EBRT and chemotherapy). No studies were identified that addressed the relative effectiveness of Gamma Knife and CyberKnife radiosurgery, and hence no conclusions may be drawn regarding comparisons between these forms of SRS.

### **Meningioma**

The methodological quality of the Level III-2 evidence identified by the current review prohibits meaningful conclusions regarding the comparative effectiveness of Gamma Knife radiosurgery (alone or in combination with surgery) and surgery in patients with meningiomas. Similarly, conclusions comparing the effectiveness of Gamma Knife and conventional radiotherapy (with or without surgery), observation, or other forms of SRS (Linac or CyberKnife) are not possible given the lack of comparative studies.

### **Pituitary adenoma**

There is Level III-2 evidence that patients with residual non-functioning pituitary adenoma after surgery benefit from Gamma Knife radiosurgery in terms of tumour progression compared with patients who are observed after surgery. However, there is no evidence comparing the rates of tumour progression in such patients undergoing radiotherapy after surgery. The methodological quality of the evidence does not permit conclusions regarding the relative effectiveness of Gamma Knife radiosurgery in terms of

post-treatment hormone function. No comparisons between Gamma Knife radiosurgery and radiotherapy (either alone or in combination with surgery) or observation alone are possible. Similarly, this review is unable to address comparisons on effectiveness between Gamma Knife and other forms of SRS (Linac and CyberKnife).

## **Cost-effectiveness**

A basic economic costing indicates that an adapted Linac unit would provide the least costly method of SRS treatment in Australia. The base case estimate for the cost per treatment for Gamma Knife radiosurgery was estimated at \$3,757 compared to a range of \$960 to \$3,549 for an adapted Linac unit, depending on the proportion of the standard Linac unit capital costs attributed. This analysis does not take into account potential differences in the effectiveness of Gamma Knife, Linac and CyberKnife radiosurgery. Furthermore, these findings are sensitive to variations in assumptions about equipment costs, working life and maintenance requirements. Further evidence about the effectiveness of Gamma Knife units versus alternatives such as adapted Linac systems is required in order to undertake a full economic analysis.

## Recommendation

---

Gamma Knife radiosurgery is safe, appears to be effective, but is not cost effective when compared with Linac stereotactic radiosurgery.

MSAC recommends that current funding arrangements should not be changed.

The Minister for Health and Ageing accepted this recommendation on 3 November 2006

# Appendix A MSAC terms of reference and membership

---

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

<b>Member</b>	<b>Expertise or Affiliation</b>
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing

Ms Samantha Robertson	Department representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

## Appendix B      Advisory panel

---

### Advisory panel for MSAC reference 34

Professor Brendon Kearney (Chair) MBBS FRACP FRACMA Director Institute of Medical & Veterinary Science Adelaide SA	Member of MSAC
Conjoint Associate Professor Michael Barton Faculty of Medicine, University of New South Wales Liverpool NSW	Royal Australian and New Zealand College of Radiologists
Professor Alan Lopez School of Population Health University of Queensland Herston QLD	Member of MSAC
Mrs Judith Maher Independent Consumer Representative Glebe NSW	Consumers' Health Forum of Australia
Dr Jeremy Millar William Buckland Radiotherapy Centre Melbourne VIC	Co-opted member
Dr Marianne Vonau Department of Neurosurgery Royal Brisbane & Women's Hospital Herston QLD	Royal Australasian College of Surgeons
Dr David Webb Australian Radiation Protection and Nuclear Safety Agency Yallambie VIC	Australian Radiation Protection and Nuclear Safety Agency
Dr Jonathan Wood Australian Association of Neurologists Artarmon NSW	Australian Association of Neurologists nominee

HTA reports/systematic reviews—cerebral metastases			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Tsao et al 2005a	<p><i>Databases:</i> Medline (1966–June 2004), Cancerlit (1975–2003), Cinahl (1982–June 2004), Embase (1980–2004 week 25).</p> <p><i>Search strategy:</i> “brain neoplasms” (MESH), “metastas#s” (text word), and “metastatic brain” combined with MESH terms “radiotherapy”, “radiotherapy, adjuvant”, “combined modality therapy”, “chemotherapy”, “surgery” and “radiosurgery”. Combined with study designs practice guidelines, meta-analyses, RCTs, clinical trials, cohort studies, retrospective studies.</p> <p><i>Other:</i> Physician Data Query clinical trials database and proceedings of ASCO (1997–2004), ASTRO (1997–2003) and ESTRO (1997–2003) searched for new/ongoing trials. Reference lists searched.</p>	<p><i>Inclusion:</i> 1) Design (published randomised or quasi-RCTs, abstracts also eligible). 2) Population (adult patients with single or multiple brain metastases from cancer of any histology). 3) Interventions (external beam radiotherapy or radiosurgery in one study arm). 4) Outcomes (survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, toxicity).</p> <p><i>Exclusion:</i> 1) Studies that used prophylactic radiotherapy for brain metastases. 2) Phase I or II, because of availability of RCTs. 3) Published in languages other than English.</p> <p><i>Application of methods:</i> Application of selection criteria and data extraction conducted by two reviewers (doesn't state independence/blinding, or dispute resolution process). Quality assessed by Jadad tool. No pooling of results undertaken for comparison of interest.</p> <p><i>Study design:</i> NHMRC level II evidence included in the review.</p> <p><i>Patients:</i> Adult patients with single or multiple brain metastases from cancer of any histology.</p> <p><i>Interventions:</i> External beam radiotherapy or radiosurgery.</p> <p><i>Comparators:</i> SRS+WBRT vs WBRT (other non-SRS comparisons also made).</p> <p><i>Outcomes:</i> Survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, toxicity.</p> <p><i>Quality criteria:</i> Jadad quality assessment tool.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes.</p> <p>Was the search adequate? —Yes.</p> <p>Was the validity of the included studies assessed? —Yes.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Included Andrews et al (2004), also considered in this review, and Kondziolka et al (1999), considered in previous MSAC review. One RCT reported in abstract form (Chougule et al 2000) not considered in either MSAC review was included.</p> <p>All patients in the SRS arms in Kondziolka et al (1999) and Chougule et al (2000) received GK. SRS patients in Andrews et al (2004) received either GK or Linac.</p> <p>Conclusions relate to patients with multiple (rather than single) brain metastases.</p>

Tsao et al 2005a cont.	<p><b>Results</b></p> <p>SRS+WBRT vs WBRT (3 RCTs)</p> <p><i>Survival and disease progression:</i></p> <p>'In summary, the radiosurgery trials showed no benefit in terms of overall survival for patients with multiple brain metastases. One-year local brain control of treated lesions have been reported to be better in patients treated with radiosurgery boost. However, in the RTOG 95-08 trial, overall time to intracranial tumour progression was no different between the two arms. The use of radiosurgery boost for selected patients with 2–4 brain metastases remain controversial.'</p> <p><i>Performance:</i></p> <p>Results from Andrews et al (2004) summarised. 'The number of patients assessed for statistical significance with respect to the outcomes of KSP, steroid use and mental status was small. The analysis was not corrected for multiple comparisons and these outcomes were not the primary endpoints of the study.'</p> <p><i>Safety:</i></p> <p>'There is a risk of toxicity with radiosurgery boost, which was reported as 3 per cent acute grades 3 and 4 toxicity and 6 per cent late grades 3 and 4 toxicities in RTOG 95-08.'</p> <p><i>Quality of life:</i></p> <p>'Overall quality of life using a validated instrument was not measured in any of the radiosurgery trials.'</p>
------------------------------	---

HTA reports/systematic reviews—cerebral metastases			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Mehta et al 2005	<p><i>Databases:</i> Medline (1990–June 2004 week 2), Cancerlit (1990–2003), Cinahl (1990–2004), Embase (1990–2004 week 25), Cochrane Library (2004 issue 2).</p> <p><i>Search strategy:</i> 1. (radiation or radiotherapy).tw 2. Radiotherapy, adjuvant/ 3. Radiosurgery/ 4. radiosurg:.tw 5. 3 or 4 6. radiotherapy.tw 7. radiation therapy.tw 8. radiat:.tw 9. 1 or 2 or 5 or 6 or 7 or 8 10. metastas#.tw 11. metastatic brain.tw 12. 10 or 11 13. exp Brain Neoplasms/ 14. 9 and 12 and 13 15. limit 14 to (human and English language and yr = 1990 = 2003) 16. 15 not child:.tw</p> <p><i>Other:</i> Physician Data Query clinical trials database and proceedings of ASCO (1997–2004), ASTRO (1997–2003) and ESTRO (1997–2003) searched for phase III RCTs. Reference lists searched.</p>	<p><i>Inclusion:</i> 1) Population (adult patients with brain metastases, any histology). 2) Design (meta-analyses, RCTs, case-control studies, prospective cohort studies, retrospective case series). 3) Intervention (use of radiosurgery, single fraction, in at least one arm, either with or without WBRT). 4) Outcomes (tumour control or response, survival, quality of life or symptom control, toxicity).</p> <p><i>Exclusion:</i> 1) Letters or editorials. 2) Case reports. 3) Published in languages other than English. 4) Studies in which results of radiosurgery for brain metastases were reported without separating newly diagnosed (previously untreated) versus recurrent lesions. 5) Any non-randomised study that included fewer than 100 newly diagnosed, previously untreated brain metastases patients (to reduce number of studies to a manageable size. For recurrent or progressive brain metastases, studies with any sample size were included). 6) Reports of patients included in multiple publications. In such cases, the most up to date report with the larger sample size was included. 7) Where it was not possible to discern the amount of overlap of patients in different studies, possible overlap was noted.</p> <p><i>Application of methods:</i> Data extracted from relevant articles in duplicate by two independent reviewers. Discrepancies resolved through discussion and with input from a third reviewer. No pooling of results undertaken. Recommendations formulated by expert panel who considered the evidence.</p> <p><i>Study design:</i> NHMRC level I–IV evidence included in the review.</p> <p><i>Patients:</i> Adult patients with single or multiple brain metastases, any histology.</p> <p><i>Interventions:</i> Radiosurgery, single fraction, either with or without WBRT</p> <p><i>Comparators:</i> SRS±WBRT vs WBRT</p> <p><i>Outcomes:</i> Tumour control or response, survival, quality of life or symptom control, toxicity</p> <p><i>Quality criteria:</i> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes.</p> <p>Was the search adequate? —Yes.</p> <p>Was the validity of the included studies assessed? —Yes, in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Included Andrews et al (2004), also considered in this review, and Kondziolka et al (1999), considered in previous MSAC review. One RCT reported in abstract form (Chougule et al 2000) not considered in either MSAC review was included.</p> <p>All patients in the SRS arms in Kondziolka et al (1999) and Chougule et al (2000) received GK. SRS patients in Andrews et al (2004) received either GK or Linac.</p> <p>Review also considered SRS vs WBRT, but most included studies compared SRS with WBRT+SRS, and hence the conclusions relate to this comparison and are not addressed here.</p>

Mehta et al 2005 cont.	<p><b>Results</b></p> <hr/> <p>SRS+WBRT vs WBRT (3 RCTs)</p> <p><i>Survival:</i></p> <p>‘There is Level I [RCT] evidence (based on one high-quality trial) to indicate that radiosurgery boost with whole-brain radiotherapy improves survival in selected patients with a single metastasis [compared with WBRT alone].’</p> <p>‘There is Level I [RCT] evidence that, for patients with multiple brain metastases, radiosurgery boost does not improve overall survival as compared with radiosurgery alone.’</p> <p><i>Disease progression:</i></p> <p>‘All three randomised trials (two fully published and one in abstract form) found a significantly improved local brain control rate with the use of radiosurgery boost as compared with whole-brain radiotherapy alone for patients with up to four metastases.’</p> <p>‘For the three randomised trials, local brain control at 1 year ranged from 82 per cent to 92 per cent in the radiosurgery boost arm vs. 0% to 71 per cent in the whole brain alone arm.’</p> <p>‘The retrospective series report a range of local brain control rates or tumour response rates at variable time points. Because of the retrospective nature of these studies, heterogeneity of patient, and treatment characteristics, conclusions regarding the impact of radiosurgery boost on brain control or tumour response as compared with patients managed with whole-brain radiotherapy alone cannot be made [based on this evidence].’</p> <p><i>Performance:</i></p> <p>‘One [randomised controlled] trial reported that the ability to taper down on steroid dose and improvement of KPS was statistically better in the radiosurgery arm at 6 months.’</p> <p>‘There is Level I [RCT] evidence that, for patients with multiple brain metastases, radiosurgery boost does not improve overall survival as compared with whole-brain radiotherapy alone. Patients eligible for radiosurgery boost in these trials had brain metastases <math>\leq 4</math> cm, KPS <math>\geq 70</math>, and up to four brain metastases.’</p> <p><i>Safety:</i></p> <p>‘There is a statistically non-significant increase in the risk of toxicity with radiosurgery boost, which was reported as 3 per cent acute Grades 3 and 4 toxicity and 6 per cent late Grades 3 and 4 toxicities in [one randomised controlled] trial.’</p> <p><i>Quality of life:</i></p> <p>‘...overall quality of life using a validated instrument was not measured in any of these trials.’</p>
------------------------------	--

HTA reports/systematic reviews—acoustic neuromas			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Yamakami et al 2003	<p><b>Gamma Knife</b> <i>Search Strategy:</i> keywords of acoustic neuroma and radiosurgery.</p> <p><b>Surgery</b> <i>Search Strategy:</i> keywords of acoustic neuroma and surgery.</p> <p><b>Conservative management</b> <i>Search Strategy:</i> Keywords of acoustic neuroma and conservative management or tumour growth.</p> <p><b>All</b> <i>Databases:</i> Medline (January 1993–January 2003) <i>Other:</i> Database searched supplemented by manual searched of original articles.</p>	<p><b>Gamma Knife</b> <i>Inclusion:</i> 1) Radiosurgery only by GK. 2) Study population <math>\geq 100</math>. <i>Exclusion:</i> Not stated.</p> <p><b>Surgery</b> <i>Inclusion:</i> 1) Study population <math>\geq 100</math>. 2) Study definition of the demographic data of patients, the outcome and complications. <i>Exclusion:</i> Large (<math>&gt;3</math> cm) acoustic neuromas.</p> <p><b>Conservative management</b> <i>Inclusion:</i> 1) Study population <math>\geq 20</math> with unilateral acoustic neuroma who underwent conservative management with radiologic follow-up. 2) Mean follow-up period <math>\geq 2</math> years. 3) Study not including recurrent tumours or tumours treated previously. <i>Exclusion:</i> Not stated.</p> <p><b>All</b> <i>Application of methods:</i> No information provided about data extraction methods (multiple reviewers etc.) <i>Study design:</i> Design of included studies not described, but appear to be case series. <i>Patients:</i> Acoustic neuroma (most patients without NF2). <i>Interventions:</i> GK, surgery, conservative management. <i>Comparators:</i> GK, surgery, conservative management. <i>Outcomes:</i> Hearing preservation, tumour progression, facial function, rate of surgery, tumour recurrence, mortality, major disability. <i>Quality criteria:</i> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes.</p> <p>Was the search adequate? —Only one database was searched. Search terms were minimal.</p> <p>Was the validity of the included studies assessed? —Yes, in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Comparisons between treatments problematic. Mean age of conservative management group was 15 years older than surgery group, and 5 years older than GK group. Measurement of pre-treatment tumour size was inconsistent between modalities, but conservative management group seemed to have smaller tumours.</p>

Yamakami et al 2003 cont.	<p><b>Results</b></p> <p>GK (9 studies, 1475 patients) Surgery (16 studies, 5005 patients) Conservative management (13 studies, 903 patients)</p> <p><b>GK vs surgery</b></p> <p><u>Useful hearing preservation:</u> GK: 66 per cent (180/271) Surgery: 49 per cent (457/926 small to medium tumours), <math>p &lt; 0.0001</math> Surgery: 36 per cent (521/1448 tumours any size), <math>p &lt; 0.0001</math> (Pearson's chi-square calculated from data in paper)</p> <p><u>Facial function:</u> GK: facial palsy in 8 per cent, trigeminal neuropathy in 8 per cent, and hydrocephalus in 3 per cent of patients Surgery: 'Good' facial function (H-B grading) in 87 per cent at 12 months after surgery Facial function measures not comparable between treatments</p> <p><b>GK vs conservative management</b></p> <p><u>Useful hearing preservation:</u> GK: 66 per cent (180/271) Conservative management: 37 per cent (22/60), <math>p &lt; 0.0001</math> (Pearson's chi-square calculated from data in paper)</p> <p><u>Tumour progression:</u> GK: Tumour grew (8%), no change (36%), regressed (56%) (mean follow-up 3.8 years) Conservative management: Tumour grew (51%), no change (47%), regressed (4%) (mean follow-up 3.1 years), <math>p &lt; 0.0001</math> (chi-square test)</p> <p><u>Rate of surgery:</u> GK: 5 per cent (32/689) Conservative management: 20 per cent (164/804), <math>p &lt; 0.0001</math> (chi-square test)</p> <p><b>Surgery (non-comparative)</b></p> <p><u>Tumour recurrence:</u> 1.8 per cent (54/2997) <u>Mortality:</u> 0.63 per cent (25/3969) <u>Major disability (permanent disability other than facial palsy or hearing disturbance):</u> 2.9 per cent (94/3290)</p>
---------------------------------	--

HTA reports/systematic reviews—primary malignant lesions			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Tsao et al 2005b	<p><i>Databases:</i> Medline (1990–June 2004 week 2), Cancerlit (1975–2003), Cinahl (1982–2004 June week 2), Embase (1980–2004 week 25), Cochrane Library (2004 issue 2).</p> <p><i>Search strategy:</i> 1. glioma.tw 2. exp radiosurgery/ 3. Gamma Knife.tw 4. stereotactic radiotherapy.tw 5. stereotactic radiation therapy 6. 2 or 3 or 4 or 5 7. 1 and 6</p> <p><i>Other:</i> Physician Data Query clinical trials database and proceedings of ASCO (1997–2004), ASTRO (1997–2003) and ESTRO (1997–2003) searched for phase III RCTs. Reference lists searched.</p>	<p><i>Inclusion:</i> 1) Population (adult patients with high-grade glioma—glioblastoma multiforme, anaplastic astrocytoma, mixed anaplastic oligoastrocytoma, anaplastic oligodendroglioma). 2) Design (meta-analyses, RCTs, case-control studies, prospective cohort studies, retrospective case series). 3) Intervention (use of radiosurgery [single fraction] or fractionated stereotactic radiotherapy in one study arm). 4) Outcomes (survival, quality of life or symptom control, tumour control or response, toxicity).</p> <p><i>Exclusion:</i> 1) Letters or editorials. 2) Case reports. 3) Published in languages other than English. 4) Studies in which results of radiosurgery or fractionated stereotactic radiotherapy were reported without separating newly diagnosed versus recurrent glioma. 5) Reports of patients included in multiple publications. In such cases, the most up to date report with the larger sample size was included. 7. In cases where it was not possible to discern the amount of overlap of patients in different studies, possible overlap was noted.</p> <p><i>Application of methods:</i> Data extracted from relevant articles in duplicate by two independent reviewers. Discrepancies resolved through discussion and with input from a third reviewer. No pooling of results undertaken. Recommendations formulated by expert panel who considered the evidence.</p> <p><i>Study design:</i> NHMRC level I–IV evidence included in the review.</p> <p><i>Patients:</i> Adult patients with high-grade glioma—glioblastoma multiforme, anaplastic astrocytoma, mixed anaplastic oligoastrocytoma, anaplastic oligodendroglioma.</p> <p><i>Interventions:</i> Radiosurgery (single fraction) or fractionated stereotactic radiotherapy (all SRS studies used prior EBRT).</p> <p><i>Comparators:</i> Surgery+EBRT+SRS vs Surgery+EBRT.</p> <p><i>Outcomes:</i> Survival, quality of life or symptom control, tumour control or response, toxicity.</p> <p><i>Quality criteria:</i> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes.</p> <p>Was the search adequate? —Yes.</p> <p>Was the validity of the included studies assessed? —Yes, in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Included Souhami et al (2004) also included in this review. Also included studies excluded from this review for using Linac-based SRS (eg, Proscio et al 2002).</p> <p>Addressed stereotactic fractionated radiotherapy also, and those results are not considered here.</p>

Tsao et al  
2005b  
cont.

## Results

Surgery+EBRT+SRS vs Surgery+EBRT (1 RCT, 5 prospective cohort studies, 7 retrospective series)

### Survival:

'There is one randomised controlled trial that provides evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU as compared with external beam radiotherapy and BCNU does not confer benefit in terms of overall survival ...'

### Disease progression:

'There is one randomised controlled trial that provides evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU as compared with external beam radiotherapy and BCNU does not confer benefit in terms of ... patterns of failure.'

'Thus there remains a lack of high quality evidence that radiosurgery boost improves brain control or tumour response in patients with newly diagnosed malignant glioma. The prospective and retrospective studies suffer from selection bias and no direct comparisons are made in terms of brain control or tumour response in patients treated with radiosurgery boost vs. not. As such, there is insufficient evidence that radiosurgery boost improves brain control/tumour response in patients with newly diagnosed malignant glioma.'

### Safety:

'There appears to be a slight increased risk of late Grade 3 toxicity with the approach of radiosurgery boost followed by external beam radiotherapy.'

'Thus there is evidence that the addition of radiosurgery boost is associated with an increased risk of toxicity ranging from significant oedema to radiation necrosis. Reoperation rates varied from approximately 19–33 per cent. A small proportion of patients subjected to reoperation had necrosis only in the operative specimens retrieved.'

### Quality of life:

'There is one randomised controlled trial that provides evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU as compared with external beam radiotherapy and BCNU does not confer benefit in terms of ... quality of life ....'

'Data on ... prospective and retrospective studies are considered insufficient to support a quality of life or symptom control benefit with the use of radiosurgery boost in patients with newly diagnosed malignant glioma.'

HTA reports/systematic reviews—primary malignant lesions			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Laperriere, Perry & Zuraw 2004	<p><u>Databases:</u> Medline (1966–June 2004), Cochrane Library (2004, Issue 2).</p> <p><u>Search strategy:</u> glioma (MESH) combined with radiotherapy (MESH), radiotherapy dosage (MESH), dose fractionation (MESH), brachytherapy (MESH), radiation-sensitising agents (MESH), radiosurgery (MESH), hypofraction:tw, hyperfraction:tw, accelerated.tw and particle.tw. Limited to practice guidelines, meta-analyses, RCTs. No language restrictions.</p> <p><u>Other:</u> Physician Data Query clinical trials database and proceedings of ASCO (1997–2004), ASTRO (1997–2003) and ESTRO (1997–2003) searched for phase III RCTs. Reference lists searched.</p>	<p><u>Inclusion:</u> 1) Meta-analyses and randomised trials comparing various aspects of radiotherapy in patients with malignant glioma. 2) Where no randomised trials were available, non-randomised studies reviewed. 3) Abstracts of trials also considered. 4) The outcome of interest was survival.</p> <p><u>Exclusion:</u> Not stated.</p> <p>Application of methods: No information on application of methods.</p> <p><u>Study design:</u> NHMRC level I–IV evidence included in the review.</p> <p><u>Patients:</u> Newly diagnosed adults with histologic confirmation of glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma.</p> <p><u>Interventions:</u> Conventional radiation, fractionated radiotherapy, hyperfractionated radiotherapy, accelerated radiotherapy, hypofractionated radiotherapy, brachytherapy, particle therapy, radiosensitisers, radiosurgery</p> <p><u>Comparators:</u> SRS+surgery+EBRT+BCNU vs surgery+EBRT+BCNU.</p> <p><u>Outcomes:</u> Survival.</p> <p><u>Quality criteria:</u> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes.</p> <p>Was the search adequate? —Only Medline and the Cochrane Library were searched.</p> <p>Was the validity of the included studies assessed? —Yes, briefly in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —No for SRS (yes for other treatments).</p> <p>The sole study included in this review was an earlier abstract report of Souhami et al (2004), also included in this MSAC review.</p> <p>This review updates an earlier review (2000), that concluded the possible advantages of SRS could not be determined based on a lack of concurrent randomised cohort studies.</p> <p>No recommendations were made regarding SRS.</p>
<b>Results</b>			
<p>SRS+EBRT+BCNU(+Surgery) vs EBRT+BCNU(+Surgery) (1 RCT)</p> <p>‘[Souhami et al 2002] detected no significant differences between treatment arms in terms of median survival, patterns of failure, quality of life deterioration and mental status. Compliance was a problem in the stereotactic radiosurgery arm with 18 per cent of patients having unacceptable deviations. Compliance was not a problem in the radiotherapy and BCNU arm.’</p> <p>‘Postoperative external beam radiotherapy is recommended as standard therapy.’</p>			

HTA reports/systematic reviews—multiple indications			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Hailey 2002	<p><u>Databases:</u> Pub Med (1997–January 24 2002), Embase (1997–September 2001), Cinahl (1997–November 2001), PsychINFO (1997–November 2001), EBM Reviews—ACP Journal Club (1991–March/April 2001), Web of Science (1997–2002), Cochrane Library (Issue 4 2001, Issue 1 2002).</p> <p><u>Search strategy:</u> (PubMed): (radiosurgery OR “stereotactic radiosurgery” OR “Gamma Knife” OR (linac OR linear accelerator* OR particle accelerators) AND (stereotactic OR stereotaxic)) AND publication type: clinical trial, meta-analysis, practice guideline, RCT, review (limited to human studies) OR in process records OR published supplied records OR case report OR comparative study OR economics OR cost and cost analysis OR treatment outcome OR outcome and process assessment (health care) OR Canada OR (radiosurgery OR “stereotactic radiosurgery” OR “Gamma Knife” (limited to human studies) AND case-control studies.</p> <p><u>Other:</u> HTA websites were searched.</p>	<p><u>Inclusion:</u> 1) Report outcomes of stereotactic radiosurgery on humans, or alternative approaches to management of the same conditions that were being treated with radiosurgery. 2) No restriction on study design. 3) No language restrictions. 4) All reports that provided details of cost or economic studies were included.</p> <p><u>Exclusion:</u> 1) Case series with &lt;20 patients. 2) Technical descriptions of apparatus, dose calculations. 3) Procedural descriptions. 4) Imaging and treatment planning approaches.</p> <p><u>Application of methods:</u> Single reviewer applied inclusion criteria and extracted data.</p> <p><u>Study design:</u> NHMRC level I–IV evidence included in the review.</p> <p><u>Patients:</u> Patients with acoustic neuromas, AVMs, cerebral metastases, primary malignant lesions, meningiomas, pituitary tumours, trigeminal neuralgia, other tumours.</p> <p><u>Interventions:</u> Stereotactic radiosurgery (GK or Linac).</p> <p><u>Comparators:</u> GK vs Linac, FSRT, surgery, WBRT.</p> <p><u>Outcomes:</u> Not stated <i>a priori</i>. Review considered relevant outcomes per indication.</p> <p><u>Quality criteria:</u> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —Yes, but specific criteria per indication not provided.</p> <p>Was the search adequate? —Yes.</p> <p>Was the validity of the included studies assessed? —Yes, in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Trigeminal neuralgia and other tumours are not discussed here.</p>
<b>Results</b>			
<b>Acoustic neuroma</b>			
GK vs FSRT (1 cohort), GK (17 case series), Linac (5 case series)			
‘Microsurgery remains the treatment of choice for many patients. SRS has a useful place in cases where surgery would have an unacceptable risk or would be refused. Long term follow up data on SRS treatments are still comparatively limited, and the methodological basis of the evidence is weak. There is still no clear evidence of the superiority of one radiotherapy/radiosurgery treatment over another.’			

Hailey 2002 cont.	<p><b>Pituitary tumours</b></p> <p>GK (12 case series), Linac (1 cohort, 2 case series)</p> <p>'A number of the studies indicated good rates of tumour control and of normalisation of hormonal levels. One series with long term follow up indicated the potential for delayed complications.'</p>
	<p><b>AVMs</b></p> <p>GK vs Surgery (1 cohort), GK (13 case series), Linac (7 case series)</p> <p>'It continues to be difficult to draw firm conclusions on the effectiveness of this technology for treatment of malformations in the absence of controlled trials. Comparisons with microsurgery are made in some of the papers, but any conclusions have to be treated with some reservation, given inevitable differences in case mix, patient selection criteria and other factors ... Rapid changes that have occurred in surgical techniques complicate longitudinal comparison of outcomes ... Lower reported complication rates after SRS cannot be readily compared with rates for other treatments as adverse events may be delayed and there have been few long term follow up studies.'</p> <p>'There is general recognition that microsurgery and SRS should be regarded as complimentary approaches to management of AVMs. Surgery is preferred if the lesion can be "safely" excised, but appropriate patient selection and level of expertise continue to cause debate. Further information is emerging on long term complications of SRS. There is no indication that either GK or Linac is superior to each other. The absence of good quality studies continues.'</p>
	<p><b>Cerebral metastases</b></p> <p>GK vs Linac (2 cohort), GK+WBRT vs WBRT (1 RCT), GK vs surgery (2 case control), GK+surgery vs surgery+WBRT (1 cohort), GK (21 case series), Linac (13 case series, 2 cohort, 1 case control)</p> <p>'These results [from 1 RCT] indicating superiority of SRS plus conventional radiotherapy over radiotherapy alone [in terms of time to local treatment failure] are supported by findings from some of the other comparative studies located ... There was no significant difference in rates of local or distant brain relapse between patients treated by Linac and those treated by GK [from one cohort study] ... Comparisons of SRS and microsurgery seem inconclusive, give[n] differences in case selection, small numbers and other methodological limitations.'</p>
	<p><b>Primary malignant lesions</b></p> <p>GK (8 case series), Linac (1 cohort, 4 case series)</p> <p>'Five studies reported treatment of gliomas, indicating relatively limited success ... Two of the studies considered treatment of children and indicated useful results for some types of brain tumour.'</p>
	<p><b>Meningiomas</b></p> <p>GK (15 case series), Linac (6 case series)</p> <p>'As with other applications of SRS, a variety of populations and clinical situations are described. It is not possible from these studies to obtain any realistic comparison between different types of SRS or between SRS and other types of treatment.'</p>

HTA reports/systematic reviews—multiple indications			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
AETMIS 2004	<p><u>Databases:</u> Medline, Cochrane Library, Embase, Healthstar. Time periods not specifically stated—‘up to the present time [20020]’.</p> <p><u>Search strategy:</u> Keywords were radiosurgery, stereotactic radiosurgery, radiotherapy, linac, accélérateur linéaire, Gamma Knife, protontherapy. Combined with cost, cost analysis and cost-effectiveness to identify economic studies.</p> <p><u>Other:</u> Searching was undertaken of unindexed reports, but the methodology was not explained.</p>	<p><u>Inclusion:</u> Criteria applied for indication, study methodology, and number of subject, but these criteria not described.</p> <p><u>Exclusion:</u> Not reported.</p> <p><u>Application of methods:</u> Number of reviewers for study selection and data extraction, and resolution of disagreements not described.</p> <p><u>Study design:</u> NHMRC Level IV evidence included in the review.</p> <p><u>Patients:</u> Patients with acoustic neuromas, vascular malformations (including AVMs), cerebral metastases, primary malignant lesions (gliomas), meningiomas, pituitary tumours (adenomas), trigeminal neuralgia, other tumours, Parkinson’s disease, epilepsy, obsessive–compulsive disorders.</p> <p><u>Interventions:</u> GK or Linac.</p> <p><u>Comparators:</u> GK vs Linac, helium ions, proton therapy.</p> <p><u>Outcomes:</u> Not stated <i>a priori</i>. Review considered relevant outcomes per indication.</p> <p><u>Quality criteria:</u> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —No.</p> <p>Was the search adequate? —Yes.</p> <p>Was the validity of the included studies assessed? —Yes, in narrative. Quality assessment not described.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>Trigeminal neuralgia, other tumours, Parkinson’s disease, epilepsy, and obsessive–compulsive disorders are not discussed here.</p> <p>Comparative cohort studies may have been included (particularly for the indications of vascular lesions and brain metastases); however, direct comparisons between treatments are not described.</p> <p>Although published in 2004, this is an English version of a report originally published in French in 2002.</p>
<p><b>Results</b></p> <hr/> <p><b>Primary malignant lesions</b> GK (2 case series), Linac (5 case series)</p> <p>‘The results of other studies of SRS for gliomas indicate widely varying efficacy ... However, all the results show that SRS is safe and effective as an adjuvant treatment for gliomas.’</p> <p>‘In short, despite the fact that there are no comparative studies from which we could compare the efficacy of the various instruments used, SRS seems to be a promising approach to the treatment of gliomas (prolongs survival in patients with malignant gliomas).’</p> <p><u>Comment:</u> Comparative survival of GK and alternative treatments not addressed. Only 2/5 included studies used GK (5/7 used Linac).</p>			

AETMIS 2004  
cont.

#### Pituitary tumours (adenomas)

GK (2 case series), Linac (2 case series), helium ions (1 case series), proton therapy (1 case series)

'Even if it seems theoretically preferable to treat pituitary adenomas with SRS (specifically, by Gamma Knife), surgical excision (microsurgery through a transsphenoidal approach) is opted for in most cases. Unlike SRS, surgical excision permits the rapid correction of hormone hypersecretion.'

'Even if the long-term follow-up results of most studies have not yet been disseminated ... it seems that SRS causes fewer complications than conventional radiotherapy.'

'[In reducing hormone hypersecretion] the Gamma Knife acts faster than conventional radiotherapy.'

'The Gamma Knife is effective in the treatment of pituitary tumours that resist surgical treatment following conventional radiotherapy and in the treatment of micro-adenomas and noncompressive sellar tumours when the patient refuses surgery or when the transsphenoidal approach is not possible.'

'As for the comparison between the linear accelerator and the Gamma Knife, to date, no scientific data support the superiority of one over the other ... it would seem that certain types of radiotherapy are more appropriate for specific types of pituitary adenomas and craniopharyngiomas. Some publications report that Gamma Knife radiosurgery is effective in the treatment of residual or recurrent craniopharyngiomas after surgical treatment.'

Comment: Unclear how conclusions were formulated. Discussion based on some studies not included in the systematic review.

#### Acoustic neuroma

GK (6 case series), Linac (3 case series)

'... SRS could be an alternative to the standard treatments (surgery and conventional radiotherapy). However, conclusions of a recent meta-analysis by Kaylie (Kaylie et al, 2000) contain certain reservations as to attributing any advantages to either of the approaches (microsurgery or Gamma Knife SRS) because of often incomplete and imprecise data and because of the lack of standards for comparing the studies with each other.'

'... SRS seems to be an appropriate therapeutic approach for VSs, given its relative safety and precision. This treatment modality, specifically the use of the Gamma Knife, could be an alternative for overcoming the interventional difficulties that the standard treatments pose and for preventing their complications.'

Comment: The basis for conclusions regarding the relative safety and precision of Gamma Knife and alternative treatments is unclear.

#### Vascular malformations (including AVMs)

SRS (5 case series. Only 1 of these used GK, and this was for cavernomas not AVMs)

Comment: Conclusions are made based on studies that are not included in the systematic review.

#### Cerebral metastases

GK (6 case series), Linac (6 case series)

'The studies are very heterogeneous. Most of them are actually case reports where the inclusion criteria are not clearly defined. Quality control or the validation process sometimes lacked methodological rigour ...'

'... all the results of the studies concerning brain metastases support the safety and efficacy of SRS in certain carefully selected cases. The main advantage of this type of treatment over conventional radiotherapy is the improvement in the patient's quality of life. However, results of randomised studies are needed before it can be categorically concluded that SRS is effective for brain metastases. In addition, SRS is still not an appropriate for adjuvant treatment to conventional radiation of the brain in patients with progressive systemic cancer.'

Comment: Conclusions appear to be based on studies that are not included in the systematic review. The comparative efficacy of GK (or SRS in general) and other treatments is not addressed.

AETMIS 2004  
cont.

### Meningiomas

GK (4 case series), Linac (6 case series)

'... Gamma Knife SRS compares with standard treatments (surgery and conventional radiotherapy alone or in combination) and permits better tumour growth control, with rates of between 87 and 100 per cent, and improved functional status, with rates from 87 to 92 per cent of patients ... Since SRS is less toxic than conventional radiotherapy, it is better suited to treatment of cavernous sinus and skull base meningiomas ... However, it is not without risks and can cause, among other things, neuropathies if administered doses are greater than 19 Gy (greater than 10 Gy in the case of ophthalmic complications due to optic nerve injury) ... However, long term results are scarce.'

'The results of studies of the treatment of meningiomas by linear accelerator are similar to those for the Gamma Knife ... Control of tumour progression varied from 89 to 98 per cent during follow-ups ranging from 23 to 48 months ... the complications observed are usually transient ... However, serious lesions (radiation necrosis together with symptomatic peritumoural edema) and deaths have been reported ...'

'SRS (by linear accelerator or Gamma Knife) seems safe and generally effective in controlling meningiomas. However, studies indicate that outcomes depend on tumour characteristics.'

Comment: Unclear how conclusions relating to the comparison between GK and standard treatments (surgery or conventional radiotherapy alone or in combination) were formulated. Conclusions relating to GK being better suited than conventional radiotherapy for treating cavernous sinus and skull base meningioma appear to be based on studies not included in the systematic review.

HTA reports/systematic reviews—multiple indications			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
MAS 2002	<p><i>Databases:</i> Cochrane Database of Systematic Reviews, DARE, Controlled Trials Register, HTA and NHS Economic Evaluation Databases, Medline (January 1998–April 2002)</p> <p><i>Search strategy:</i> Search terms were Gamma Knife, efficacy, cost-effectiveness.</p> <p><i>Other:</i> Not stated.</p>	<p><i>Inclusion:</i> Not stated.</p> <p><i>Exclusion:</i> Reviews, use of SRS for conditions not included in this analysis, insufficient data reported in abstract, report had been included in the MSAC review.</p> <p><i>Application of methods:</i> Review updated previous MSAC assessment. No application of methods described.</p> <p><i>Study design:</i> NHMRC Level I–IV evidence included in the review.</p> <p><i>Patients:</i> Patients with AVMs, acoustic neuromas, cerebral metastases, and trigeminal neuralgia.</p> <p><i>Interventions:</i> GK.</p> <p><i>Comparators:</i> GK vs Linac, surgery.</p> <p><i>Outcomes:</i> Not stated <i>a priori</i>. Review considered relevant outcomes per indication.</p> <p><i>Quality criteria:</i> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question? —No.</p> <p>Was the search adequate? —Limited search terms used. Only one electronic database searched (Medline).</p> <p>Was the validity of the included studies assessed? —No discussion of study validity. No quality criteria presented.</p> <p>Are sufficient details about the individual included studies presented? —Yes.</p> <p>This review updated the previous MSAC assessment by extending the search until April 2002. However, the search strategy was not extensive, and it is likely that some studies were missed. This is a 'rapid response HTA'.</p> <p>Levels of evidence in this review defined as follows: Level 1 (large RCT or systematic review of RCTs), Level 2 (small RCT), Level 3 (non-randomised trial, database or register studies, case series or retrospective review). Trigeminal neuralgia not discussed here.</p>
<b>Results</b>			
<p><b>Acoustic neuroma</b></p> <p>Linac (1 case series)</p> <p>'There is no evidence that there is any difference in effectiveness between Gamma Knife and Linac-based SRS in the treatment of AVM or acoustic neuroma.'</p> <p>'There is level 3 evidence that microsurgery remains the best overall treatment option for AVM and acoustic neuroma.'</p> <p>'Irrespective of whether SRS is performed using Gamma Knife or Linac, there is level 3 evidence that it is an important technology for surgically inaccessible acoustic neuroma and AVM lesions or for lesions considered to present a significant surgical risk.'</p> <p>'There is level 3 evidence that, in the treatment of acoustic neuroma, fractionated Linac-based SRS results in fewer facial nerve complications than Gamma Knife.'</p>			

MAS 2002  
cont.

#### AVMs

GK (3 case series)

'There is no evidence that there is any difference in effectiveness between Gamma Knife and Linac-based SRS in the treatment of AVM or acoustic neuroma.'

'There is level 3 evidence that microsurgery remains the best overall treatment option for AVM and acoustic neuroma.'

'Irrespective of whether SRS is performed using Gamma Knife or Linac, there is level 3 evidence that it is an important technology for surgically inaccessible acoustic neuroma and AVM lesions or for lesions considered to present a significant surgical risk.'

---

#### Cerebral metastases

GK (2 case series), GK or Linac (1 cohort), WBRT+SRS vs WBRT (1 RCT, SRS modality not stated)

'... there is level 1 evidence that there is no benefit for SRS compared to WBRT when employed as a first line radiation treatment.'

'There is level 3 evidence that SRS is beneficial in the treatment of recurrent primary brain tumours or metastases following front line radiation therapy.'

'There is level 3 evidence that when employed for recurrent brain metastases, Gamma Knife SRS provides improved control of local regional progression than Linac-based SRS. However, the study reporting this observation observed that despite a 13 per cent improvement in symptom control, 22 per cent of patients experienced severe neurotoxicity which was irreversible in 42 per cent of cases, and 3 per cent of all cases died as a result of neurotoxicity attributed to SRS.'

HTA reports/systematic reviews—multiple indications			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Mitchell 2001	<p><i>Databases:</i> Medline (1966–October 2001), Embase (1980–October 2001), Cochrane 2001 Issue 3, DARE, NHS Health Technology assessment Database, NHS Economic Evaluation Database. Search date: October 2001.</p> <p><i>Search strategy:</i> Not stated</p> <p><i>Other:</i> Not stated.</p>	<p><i>Inclusion:</i> Not stated.</p> <p><i>Exclusion:</i> Not stated.</p> <p><i>Application of methods:</i> Review updated a previous systematic review, published in 1998. Inclusion of studies performed by two reviewers.</p> <p><i>Study design:</i> NHMRC Level I–IV evidence included in the review.</p> <p><i>Patients:</i> Patients with AVMs, acoustic neuromas, and cerebral metastases.</p> <p><i>Interventions:</i> GK.</p> <p><i>Comparators:</i> GK vs ‘conventional techniques’.</p> <p><i>Outcomes:</i> Not stated <i>a priori</i>. Review considered relevant outcomes per indication.</p> <p><i>Quality criteria:</i> Not stated.</p>	<p>Were inclusion/exclusion criteria reported that addressed the review question?</p> <p>—No.</p> <p>Was the search adequate?</p> <p>—The search strategy not presented.</p> <p>Was the validity of the included studies assessed?</p> <p>—Yes.</p> <p>Are sufficient details about the individual included studies presented?</p> <p>—Data extraction tables are not presented.</p> <p>This review did not consider GK separately from other SRS modalities. The review updated a previous systematic review published in 1998.</p>
<b>Results</b>			
<b>Acoustic neuroma</b>			
SRS (1 systematic review, 1 case series)			
‘... the level of evidence was poor. However, the studies included in the systematic review indicate a possible benefit through good local control (in many cases a surrogate end point for functional outcome) and acceptable longer term outcomes. This conclusion should be regarded as tentative in the absence of comparative studies.’			
<b>AVMs</b>			
SRS (1 systematic review, 8 case series)			
‘... in the absence of comparative studies, effects of treatment compared with alternative management strategies remain uncertain.’			
<b>Cerebral metastases</b>			
SRS (1 systematic review, 2 cohort studies)			
‘The review [included in this HTA] stated that stereotactic radiosurgery may have similar functional effects compared with conventional techniques. However, given the lack of controlled studies, this conclusion must be regarded as tentative.’			
‘Overall, subsequent case series found that stereotactic radiosurgery may provide good local control with low morbidity. Few complications were detected, and some studies indicated an improved quality of life with stereotactic radiosurgery. The case series design is particularly susceptible to bias and confounding, and results should be regarded as tentative.’			

Randomised controlled trials—cerebral metastases										
Level	Author & year	Study design	N	Participant characteristics	Outcomes				Quality	
II	Andrews et al 2004	<p><i>Design:</i> Multicentre RCT.</p> <p><i>Primary outcome:</i> Survival.</p> <p><i>Secondary outcomes:</i> Tumour response and local rates, overall intracranial recurrence rates, cause of death, performance measurements.</p> <p><i>Randomisation:</i> Patients stratified by number of brain metastases (1 vs 2–3) and extent of extracranial disease (none vs present). Randomisation within strata by permuted blocks with computerised techniques at a single centre.</p> <p><i>Sample size calculation:</i> Designed to detect 50% improvement in median survival time from 7.1 to 10.6 months after treatment with 80% power; also a 75% improvement in median survival time in single brain metastases patients with 80% power.</p> <p><i>Interventions(s):</i> SRS delivered by both Gamma Knife and Linac-based systems.</p> <p>Metastases ≤2cm treated with surface isodose prescription of 24.0 Gy; metastases &gt;2cm and ≤3cm with 18.0 Gy; and metastases &gt;3cm and ≤4cm with 15.0 Gy.</p> <p><i>Analysis:</i> Intention to treat.</p>	N = 333 WBRT + SRS (GK or Linac) = 164 WBRT = 167  Cannot determine proportions of Linac and GK patients.	<p><i>Inclusion:</i> 1) Confirmed systemic malignant disease. 2) Aged 18 years or more. 3) No previous cranial radiation. 4) Contrast enhanced MRI showing 1–3 brain metastases with a maximum diameter of 4 cm for the largest lesion and 3 cm for additional lesions.</p> <p><i>Exclusion:</i> 1) KPS &lt;70. 2) Haemoglobin concentration &lt;80 g/L. 3) Absolute neutrophil count &lt;50 000 cells/μL. 4) Platelet count &lt;50 000 cells/μL. 5) Metastases in brain stem or within 1 cm of optic apparatus. 6) Treatment for systemic cancer with 1 month of enrolment.</p> <p>Mean age for WBRT + SRS: 58.8 (range, 19–82). Mean age for WBRT: 59.9 (range, 24–90).</p> <p>Males/females (WBRT + SRS): 52%/48%. WBRT: 53%/47%.</p> <p>Treatment groups appear to be balanced on age, size of largest metastasis, primary tumour site, neurological function, RPA class, KPS, control of primary site, extracranial metastases, number of brain metastases, and MMSE, but statistical comparisons not presented.</p>	<p><b>Survival</b> (mean months)</p> <p>Overall</p> <p>Single metastasis</p> <p>Largest tumour &gt;2cm</p> <p>RPA class 1</p> <p>Squamous/NSCLC</p> <p>KPS 90–100</p> <p>Brain alone</p> <p>Brain +1 extracranial</p> <p>Brain +2 extracranial</p> <p>Overall (GK vs Linac)</p> <hr/> <p><b>Local control</b></p> <p>Time to progression</p> <p>Local control rates</p> <hr/> <p><b>Performance</b></p> <p>KPS improved</p> <p>Steroid use decreased</p> <p>MMSE improved</p>	WBRT+ SRS	WBRT	WBRT+ Linac	<p>ρ</p> <p>0.1356</p> <p>0.0390</p> <p>0.0449 (ns)</p> <p>0.0453 (ns)</p> <p>0.0508</p> <p>0.0714</p> <p>0.5207</p> <p>0.1686</p> <p>0.8245</p> <p>0.9415</p> <hr/> <p>ρ</p> <p>0.1278</p> <p>0.0132</p> <hr/> <p>ρ</p> <p>0.0331</p> <p>0.0158</p> <p>ns</p>	<p>Comparator is WBRT, not GK alone or surgery +/- WBRT. Cannot determine proportions of Linac and GK patients.</p> <p>2 patients excluded from study.</p> <p>31/164 patients (19%) allocated to WBRT+SRS group did not undergo SRS.</p> <p>Subgroups other than single metastases (included in sample size calculations) adjusted for multiple comparisons (<math>p = 0.0056</math>); however, performance analyses (KSP, steroid use, MMSE) were not.</p> <p>Protocol deviations in a small proportion of SRS+WBRT patients (unable to calculate exact figures).</p> <p>Comparisons between GK and Linac are not randomised.</p>

<u>Safety (acute)</u>	WBRT+ SRS	WBRT
Worst reported toxicity grade		
1	43%	36%
2	18%	26%
3	2%	0%
4	1%	0%
Nausea/vomiting		
	17%	16%
Hearing loss		
	1%	2%
Skin (acute)		
	46%	46%
Skin (sub-acute)		
	7%	5%
Neuro (central)		
	16%	12%
Neuro (peripheral)		
	5%	3%
Other		
	14%	12%
<u>Safety (late)</u>	WBRT+ SRS	WBRT
Worst reported toxicity grade		
1	14%	14%
2	6%	7%
3	3%	2%
4	3%	1%
Nausea/vomiting		
	4%	3%
Hearing loss		
	4%	4%
Skin (chronic)		
	4%	13%
Neuro (central)		
	14%	6%
Neuro (peripheral)		
	4%	0%
Other		
	5%	2%



Ototoxicity	2%	2%
Skin	23%	17%
Neurologic	15%	9%
Other	23%	22%

Controlled trials—meningiomas						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality
III-2	Hart & Giannotta 2003	<p><i>Design:</i> Retrospective, consecutive cohort.</p> <p><i>Outcomes:</i> Neurologic deficit, hospital stay, tumour control.</p> <p><i>Intervention(s):</i></p> <p>GK: patients treated in single fractions by a cobalt-60 201-source Leksell model C Gamma Knife. Mean max radiosurgical dose of 30.8 Gy (range 28–32) to the tumour centre, and mean margin dose of 15.4 Gy (range 14–16).</p> <p>Surgery: Single sitting surgical aim was gross total resection.</p> <p>Staged surgical aim was maximal debulking, leaving behind only tumour that could be reached with confidence in a second approach from a different corridor.</p> <p>Surgery with GK aimed for cytoreduction with residual tumour volume treatable by GK. GK followed surgery by 8–12 weeks in most cases.</p> <p><i>Follow-up:</i> Mean 69.8 months (range 51–84) radiographic follow-up of tumour progression.</p>	<p>N = 26</p> <p>Single sitting surgery = 9</p> <p>Staged surgery = 6</p> <p>GK+Surgery = 11</p>	<p><i>Inclusion:</i> Patients with large, non-compartmental meningioma (measuring at least 4 cm in one or more linear dimension and involving more than one anatomic region of the skull base).</p> <p>All tumours originated along the central axis of the skull base and involved, to a greater or lesser extent, the clivus, petrous bone, cavernous sinus, and/or medial sphenoid wing.</p> <p>Demographic characteristics not presented. Comparability of the groups not discussed.</p>	<p><i>Cranial nerve deficits:</i> 3/9 (33%) in single sitting surgery group, 3/11 (27%) in surgery+GK group, 1/6(16%) in staged surgery group.</p> <p><i>Major neurological deficits:</i> 2/9 (22%) in single sitting surgery group. No major neurological deficits in staged surgery and surgery+GK groups. Major neurological deficits defined as any type of hemi- or tetraparesis, or plegia, visual loss or field defect, alteration in level of consciousness, cognitive deficit, aphasia or dysphasia etc.</p> <p><i>Mortality:</i> 1/9 (11%) mortality in single sitting surgery group. No deaths in staged surgery and surgery+GK groups.</p> <p><i>Tumour control:</i> 2/11 (18%) recurrence in surgery+GK group. No recurrence in single or staged surgery groups.</p>	<p>Small sample size.</p> <p>Study not randomised, and comparability of the groups is not discussed. Likely selection bias.</p> <p>Follow-up noted to be inadequate for assessing the effects of GK.</p> <p>'[It is] difficult to state definitively that 1 particular treatment plan is superior to another'.</p>

Controlled trials—meningiomas						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality
III-2	Pollock et al 2003	<p><i>Design:</i> Retrospective, consecutive cohort.</p> <p><i>Outcomes:</i> Tumour control, additional treatment, patient symptoms, complications.</p> <p><i>Intervention(s):</i></p> <p>GK: Leksell Gamma Knife. Mean max radiosurgical dose of 34.9 Gy and mean margin dose of 17.7 Gy. Mean number isocentres 8 (range 1–15).</p> <p>Surgery: Resections were Grade 1 (42%), Grade 2 (42%), and Grade 3–4 (16%).</p> <p><i>Follow-up:</i> Surgical follow-up at 3 months then yearly. GK follow-up at 6, 12, 24, 48 months then biannually.</p> <p>Mean follow up for GK (63.5 months, range 24–125) not significantly different from surgery (64.2 months, range 1–132).</p>	<p>N = 198</p> <p>GK = 62</p> <p>Surgery = 136</p>	<p><i>Inclusion:</i> Patients undergoing GK or surgery as primary treatment for benign meningiomas &lt;35 mm in average diameter.</p> <p><i>Exclusion:</i> 1) Average tumour diameter &gt;35 mm, recurrent tumour, atypical/malignant histological features, surgery limited to biopsy.</p> <p><i>Mean age (years):</i> GK (57.8), Surgery (52.7) (<math>p = 0.03</math>)</p> <p><i>Preoperative cranial nerve deficit:</i> GK (66%), surgery (42%) (<math>p = 0.002</math>)</p> <p><i>Preoperative seizure:</i> GK (0%), surgery (11%) (<math>p = 0.02</math>)</p> <p><i>Skull base location:</i> GK (89%), surgery (70%) (<math>p = 0.01</math>)</p> <p><i>Convexity location:</i> GK (3%), surgery (18%) (<math>p = 0.01</math>)</p> <p>Treatment groups balanced on gender, tumour size, follow-up.</p>	<p><i>Tumour recurrence/progression:</i> Overall: GK (2%) vs surgery (11%) (<math>p = 0.04</math>).</p> <p><i>Progression-free survival:</i> GK (3-year = 100%, 7-year = 95%) vs Grade 1 resections (3-year = 100%, 7-year = 96%) (<math>p = 0.094</math>); vs Grade 2 resections (3-year = 91%, 7-year = 82%) (<math>p &lt; 0.05</math>); vs Grade 3–4 resections (3-year = 68%, 7-year = 34%) (<math>p &lt; 0.001</math>).</p> <p><i>Additional treatment:</i> GK (3%) vs surgery (16%) (<math>p = 0.02</math>).</p> <p><i>Symptom improvement:</i> GK (13%) vs surgery (13%) (<math>p = 1.00</math>).</p> <p><i>Complications:</i> GK (10%) vs surgery (22%) (<math>p = 0.06</math>).</p> <p>GK: diplopia, facial/numbness/pain, cyst formation requiring placement of cysto-peritoneal shunt, stroke secondary to carotid artery occlusion.</p> <p>Surgery: New cranial nerve deficits, new seizures, hemiparesis, subdural haematoma requiring evacuation, visual field loss, craniotomy flap migration requiring cranioplasty.</p>	<p>Study not randomised, and significant differences in patient characteristics between groups. Likely selection bias.</p> <p>Follow-up noted to be inadequate for assessing the effectiveness and safety of GK.</p> <p>Comparisons between GK and subgroups of surgical resection not adjusted for multiple comparisons.</p>

Controlled trials—meningiomas																						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality																
III-2	Linskey, Davis, & Ratanatharathorn 2005	<p><i>Design:</i> Retrospective, consecutive cohort.</p> <p><i>Outcomes:</i> Tumour control, performance, neurologic symptoms, complications, patient satisfaction.</p> <p><i>Intervention(s):</i> GK: Leksell model B Gamma Knife. Mean margin dose of 16.4 Gy (range 14–20 Gy). Mean number isocentres 15.9 (range 1–36). Surgery: Resections were Grade 1 (71%), Grade 2 (17%), and Grade 3–4 (11%). <i>Follow-up:</i> Median 2 years, range 1 day–5 years).</p>	<p>N (patients) = 64</p> <p>Treatments reported by number of operations (N = 74); GK = 38 Surgery = 35 (Surgery of tumour ≤3 cm = 18) Stereotactic biopsy = 1</p> <p><i>Benign:</i> n = 61 GK = 31 Surgery = 30</p> <p><i>Atypical/malignant:</i> n = 12 GK = 7 Surgery = 5</p>	<p><i>Inclusion:</i> Patients with meningiomas treated with GK, surgical resection or stereotactic biopsy.</p> <p><i>Exclusion:</i> 1) Known history of primary cancer or hemangiopericytoma. 2) Tumours other than meningiomas.</p> <p><i>Mean age (years):</i> GK (60.0, range 23–85) vs surgery (50.7, range 4 months–79 years) (<math>p = 0.0223</math>); vs surgery ≤3 cm (43.85, range 4 months–79 years).</p> <p><i>Mean tumour volume:</i> GK (7.85 mm<sup>3</sup>, range 0.49–39.6) vs surgery (44.4 mm<sup>3</sup>, range 0.52–179.6) (<math>p = 0.0078</math>).</p> <p><i>History of failed treatment:</i> GK (55.3%) vs surgery (14.3%) (<math>p &lt; 0.0001</math>).</p> <p><i>Mean KPS:</i> GK (84.76, range 60–100) vs surgery ≤3 cm (91.11, range 80–100) (<math>p = 0.0321</math>); vs surgery (87.42, range 60–100).</p> <p>Tumours arising from the convexity, sphenoidal ridge without cavernous sinus involvement, and the posterior fossa more likely to undergo surgery.</p> <p>Cavernous sinus and petroclival tumours as well as those involving the Torcular herophili more likely to undergo GK.</p> <p>Treatment groups balanced on gender and atypical/malignant histological status.</p>	<p><i>Tumour recurrence/progression:</i> <i>Benign tumours:</i> Overall: GK (3.2%) vs surgery (6.7%) (<math>p = ns</math>). GK (3.2%) vs grade 1 or 2 resections (0.0%) (<math>p = ns</math>)</p> <p><i>Atypical/malignant tumours:</i> Overall: GK (33%) vs surgery (20%) (<math>p = ns</math>).</p> <p><i>Average KPS improvement:</i> GK (from 87 to 92) vs surgery (84 to 86) (neither improvement significant).</p> <p><i>Neurological symptoms:</i></p> <table border="1"> <thead> <tr> <th></th> <th>GK</th> <th>Surgery</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Improved</td> <td>43%</td> <td>24%</td> <td>&lt;0.0001</td> </tr> <tr> <td>Unchanged</td> <td>43%</td> <td>63%</td> <td></td> </tr> <tr> <td>Worsened</td> <td>13%</td> <td>14%</td> <td>ns</td> </tr> </tbody> </table> <p>Symptoms worsening for GK: mild visual field deficits, hemi paresis, seizures, mild conductive hearing loss.</p> <p>Symptoms worsening for surgery: cavernous sinus cranial neuropathies, new frontal lobe symptoms, subtle memory disturbance.</p> <p><i>Complications:</i> No procedure-related 30-day mortality or major permanent neurological morbidity in either group.</p> <p>GK: cervical spinal cord syrinx, temporary hemiparesis and new seizures, temporary worsening visual field/acuity, focal scalp numbness, focal scalp alopecia, V<sub>1</sub> shingles.</p> <p>Surgery: Epidural abscess, asymptomatic resection cavity haematoma, deep venous thrombosis, bilateral temporal lobe HSV encephalitis, temporary frontalis nerve paresis, persistent periincisional scalp numbness.</p> <p><i>Patient satisfaction:</i> Satisfied and would have procedure again: GK (91%) vs surgery (92%) (<math>p = ns</math>) Recommend same procedure to family and friends: GK (91%) vs surgery (92%) (<math>p = ns</math>)</p>		GK	Surgery	p	Improved	43%	24%	<0.0001	Unchanged	43%	63%		Worsened	13%	14%	ns	<p>Study not randomised, and significant differences in patient characteristics between groups. Selection bias evident due to different recommended treatment strategies for GK and surgery.</p> <p>Results analysed by tumour rather than by patient.</p> <p>Results of atypical malignant tumours based on small patient numbers (lower than eligibility criteria for this review).</p> <p>Follow-up noted to be inadequate for assessing the effectiveness and safety of GK.</p>
	GK	Surgery	p																			
Improved	43%	24%	<0.0001																			
Unchanged	43%	63%																				
Worsened	13%	14%	ns																			

Controlled trials—pituitary adenoma						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality
III-2	Ikeda, Jokura & Yoshimoto 2001	<p><i>Design:</i> Retrospective(?) cohort.</p> <p><i>Outcomes:</i> Remission, complications.</p> <p><i>Intervention(s):</i></p> <p>GK: Mean marginal dose 25 Gy (range 16.6–35). Treatment plan standard dose to tumour margin 25 Gy. Inside target periphery tumour dose increases to 20–40 Gy. Treatment plan limited dose to optic apparatus to &lt;10 Gy. Patients underwent GK at &gt;6 months after surgery.</p> <p>Surgery: Transsphenoidal surgical adonectomy performed via the sublabial approach.</p> <p><i>Follow-up:</i></p> <p>Endocrinological: Surgical follow-up at 3 weeks and 6 months. GK follow-up at 6, 12, 18, 24 months then annually.</p> <p>Residual tumour volume: Surgical follow-up at &gt;6 months then annually. GK follow-up at 6, 12, 18, 24 months then annually.</p> <p>Mean follow-up for GK 59 months (range 18–106). Cannot determine mean follow-up for surgical group.</p>	<p>N= 90</p> <p>Surgery+GK = 18</p> <p>Surgery = 72</p>	<p><i>Inclusion:</i> Patients undergoing transsphenoidal surgery for GH-secreting pituitary adenoma (GH level &gt;3 ng/ml, elevated insulin-like growth factor-I level, evidence of sellar mass on MR) between January 1989 and March 2000.</p> <p><i>Exclusion:</i> Not stated.</p> <p><i>Mean age (years):</i></p> <p>Surgery+GK: 40 (range 26–66)</p> <p>Surgery: 49 (range 11–75)</p> <p>(Mean ages for treatment groups imputed from data presented. No statistical comparison possible).</p> <p><i>Gender:</i></p> <p>Surgery+GK: 28% males, 72% females</p> <p>Surgery: 51% males, 49% females</p> <p><math>p = 0.07</math> (Pearson's chi-square calculated from data in paper. Percentages imputed from data presented).</p> <p>No further information about comparability of treatment groups.</p>	<p><i>Remission:</i></p> <p>Surgery: 60/90 (67%) biochemical cure</p> <p>Surgery+GK: 14/17 (82%) biological cure. 1 patient lost to follow-up.</p> <p>(<math>p = 0.03</math>, chi-square calculated from data in paper).</p> <p><i>Complications:</i></p> <p>No perioperative mortality in either group.</p> <p>No aggravation of pituitary dysfunction after either surgery or GK.</p> <p>Visual function (acuity and visual field) and eye movement normal in all patients after GK.</p>	<p>Study not randomised. Comparability between groups cannot be assessed. Selection bias present in that all patients undergoing GK had surgical treatment failure. Patients likely to differ on other characteristics.</p> <p>Results for surgery consider all 90 patients, and results from surgery+GK include a subset of 18 of these patients. Hence, comparisons are not between 2 different groups.</p> <p>Different definitions of remission applied to treatment groups. Surgery used biochemical remission (normalisation of insulin-like growth factor-I level within 6 months, or fall in serum GH below 1 ng/ml after oral glucose 75 g). GK used biological definition (normalisation of age-adjusted insulin-like growth factor-I level).</p>

Controlled trials—pituitary adenoma						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality
III-2	Picozzi et al 2005	<p><i>Design:</i> Retrospective cohort.</p> <p><i>Outcomes:</i> Tumour recurrence.</p> <p><i>Intervention(s):</i></p> <p>GK: Mean margin dose of 16.5 Gy (range 13–21). Maximum dose to optic pathway &lt;8 Gy in 73% of patients, but above 10 Gy in 18% to allow complete tumour coverage. GK performed within 1 year after surgery.</p> <p>Surgery: Maximal surgical debulking.</p> <p><i>Follow-up:</i> MR follow-up yearly after surgery, and at 6, 12, 24, 36, 48 months then biannually after GK+surgery.</p> <p>Mean follow up for GK+surgery (40.6 months, range 2–94) not significantly different from surgery (41.6 months, range 12–108) (p = 0.83).</p>	<p>N = 119</p> <p>GK+Surgery = 51</p> <p>Surgery = 68</p>	<p><i>Inclusion:</i> All patients had residual non-functioning pituitary adenomas evident on MR after surgery. No patients had clinical or biochemical evidence of hormone hypersecretion.</p> <p><i>Exclusion:</i> 1) Follow-up &lt;1 year. 2) Those treated with GK only after tumour recurrence.</p> <p>Treatment groups balanced on age, gender, number of previous operations, gonadotropinoma, tumour size, and follow-up.</p>	<p><i>Tumour recurrence/progression:</i></p> <p>Surgery+GK (3.9%)</p> <p>Surgery (47.1%) (p&lt;0.001)</p> <p><i>5-year progression-free survival:</i></p> <p>Surgery+GK—89.8% (95% CI: 76.2–100%)</p> <p>Surgery—51.1% (95% CI: 37.5–64.8%)</p> <p>(p-value not reported. 'At 5-years, the estimated recurrence-free survival in patients who underwent GKS was significantly higher than in the group that received no postoperative treatment').</p>	<p>Study not randomised, but treatment groups appear to be well balanced.</p>

Controlled trials—acoustic neuroma																		
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality												
III-2	Myrseth et al 2005	<p><u>Design:</u> Retrospective, consecutive cohort.</p> <p><u>Outcomes:</u> Tumour control, facial nerve function, complications, quality of life.</p> <p><u>Intervention(s):</u></p> <p>GK: Mean maximal dose was 35.3 Gy (range 17–40). Mean tumour margin dose was 12.2 Gy (range 10–20).</p> <p>Surgery: Suboccipital surgery used modified supine/lateral position and craniectomy, or three-quarters prone position and craniotomy. Translabyrinthine surgery performed with patient in supine position.</p> <p><u>Follow-up:</u> mean follow-up 5.9 years (range 1.0–14.2). Not significantly different between treatment groups.</p>	<p>N = 189</p> <p>GK = 103</p> <p>Surgery = 86</p>	<p><u>Inclusion:</u> Patients with acoustic neuroma treated with GK or surgical resection.</p> <p><u>Exclusion:</u> Non-Norwegian patients due to incomplete data.</p> <p><u>Mean age (years):</u> GK (59.7, range 22–82) vs surgery (50.1, range 25–83) (<math>p &lt; 0.001</math>).</p> <p><u>Pre-treatment hearing deficit:</u> GK (90.2%) vs surgery (97.6%) (<math>p = 0.036</math>).</p> <p><u>Tumour diameter:</u></p> <table border="1"> <thead> <tr> <th>mm</th> <th>Surgery</th> <th>GK</th> </tr> </thead> <tbody> <tr> <td>0–10</td> <td>30.2%</td> <td>17.5%</td> </tr> <tr> <td>11–20</td> <td>38.4%</td> <td>66.0%</td> </tr> <tr> <td>21–30</td> <td>31.4%</td> <td>16.5%</td> </tr> </tbody> </table> <p><math>p &lt; 0.001</math> (chi-square calculated from data in paper)</p> <p>Therapy given according to patient preference, but GK recommended for elderly patients, those with serious additional disease, or if hearing loss after treatment associated with serious discomfort due to occupation/social life.</p> <p>Treatment groups balanced on number of patients alive/dead, and pre-treatment tinnitus, vertigo and trigeminal affection.</p>	mm	Surgery	GK	0–10	30.2%	17.5%	11–20	38.4%	66.0%	21–30	31.4%	16.5%	<p><u>Tumour control:</u></p> <p>GK = 91/102 (89.2%)</p> <p>Surgery = 81/86 (94.2%)</p> <p>(<math>p = 0.2</math>, chi-square calculated from data in paper)</p> <p><u>Post-treatment facial nerve function (Grade 1–2):</u></p> <p>GK = 91/96 (94.7%)</p> <p>Surgery = 67/84 (79.8%)</p> <p><math>p = 0.0026</math></p> <p><u>Complications:</u></p> <p>GK: 4/102 (3.9%) developed hydrocephalus/enlarged ventricles.</p> <p>Surgery: Overall 40/86 (46.5%) complications, including 1 postoperative death; also cerebrospinal fluid leak, intracranial haematoma, meningitis, brainstem lesion, pneumonia, pulmonary embolus, subcutaneous abdominal haematoma from fat tissue harvesting.</p> <p><u>SF-36 (QoL):</u></p> <p>Significantly greater deviations below Norwegian norms in the surgery group than the GK group for physical functioning (<math>p = 0.026</math>), role–physical categories (<math>p = 0.04</math>), and role–emotional (<math>p = 0.003</math>). No difference between bodily pain, general health, vitality, social functioning and mental health categories.</p> <p><u>Glasgow Benefit Inventory (QoL):</u></p> <p>GK patients scored significantly higher than surgical patients overall, and on ‘general and psychosocial health’ category. No difference in ‘social support’ and ‘physical health status’ between treatment groups.</p>	<p>Study not randomised, and significant differences in patient characteristics between groups. Selection bias evident due to different recommended treatment strategies for GK and surgery.</p> <p>5 patients in surgical group received additional GK.</p> <p>5 patients in GK group received additional surgery.</p>
mm	Surgery	GK																
0–10	30.2%	17.5%																
11–20	38.4%	66.0%																
21–30	31.4%	16.5%																

Controlled trials—acoustic neuroma																		
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality												
III-2	Karpinos et al 2002	<p><u>Design:</u> Retrospective cohort.</p> <p><u>Outcomes:</u> Tumour control, hearing preservation, development of cranial neuropathies, complications, functional outcome, patient satisfaction.</p> <p><u>Intervention(s):</u> GK: Patients treated by a cobalt-60 201-source Leksell model U Gamma Knife. Mean central tumour dose was 28.6 Gy (range 20–48). Mean tumour margin dose was 14.5 Gy (range 10–24). Surgery: Surgery performed by suboccipital, translabyrinthine or middle fossa approaches.</p> <p><u>Follow-up:</u> GK: mean follow-up 46.7 months (range 3–84). Surgery: Mean follow-up 31 months (range 3–72). Follow-up appears to be longer in GK group, but statistical comparisons not reported.</p>	<p>N = 96</p> <p>GK = 73</p> <p>Surgery = 23</p>	<p><u>Inclusion:</u> Patients with acoustic neuroma treated with GK or surgical resection.</p> <p><u>Exclusion:</u> Patients with neurofibromatosis had bilateral tumours and were excluded.</p> <p><u>Mean age (years):</u> GK (61.6, range 34–84) vs surgery (44.8, range 17–75) (<math>p &lt; 0.05</math>).</p> <p><u>Tumour size:</u></p> <table border="1"> <thead> <tr> <th>(mm)</th> <th>Surgery</th> <th>GK</th> </tr> </thead> <tbody> <tr> <td>&lt;20</td> <td>34.8%</td> <td>74.0%</td> </tr> <tr> <td>20–39</td> <td>39.1%</td> <td>23.3%</td> </tr> <tr> <td>&gt;40</td> <td>26.1%</td> <td>2.7%</td> </tr> </tbody> </table> <p><math>p &lt; 0.05</math></p> <p>Patients eligible for surgery if had worsening symptoms, enlargement of tumour, regrowth after previous resection in younger patients, tumour enlargement after GK, and patient preference.</p> <p>Patients eligible for GK if increasing symptoms and &gt;40 years old, couldn't undergo surgery, tumour in only hearing ear, bilateral acoustic tumours, recurrence after previous resection, and refusal of surgery.</p> <p>Treatment groups balanced on gender, tumour location, prior treatment, and signs and symptoms.</p>	(mm)	Surgery	GK	<20	34.8%	74.0%	20–39	39.1%	23.3%	>40	26.1%	2.7%	<p><u>Tumour control:</u> GK = 50/55 (91%) Surgery = 14/14 (100%) (<math>p &gt; 0.05</math>)</p> <p><u>Preservation of serviceable hearing:</u> GK = 4/9 (44%) Surgery = 2/5 (40%) (<math>p = 0.227</math>)</p> <p><u>Preservation of any measurable hearing:</u> GK = 23/40 (57%) Surgery = 2/14 (14%) (<math>p = 0.01</math>)</p> <p><u>Complete hearing loss (among those with some measurable hearing pre-treatment):</u> GK = 14/40 (35%) Surgery = 12/14 (86%) (<math>p = 0.001</math>, Fisher's exact calculated from data in paper)</p> <p><u>Post-treatment facial nerve function (grade 1–2):</u> GK = 38/49 (77.6%) Surgery = 6/17 (35.3%) (<math>p = 0.001</math>, chi-square calculated from data in paper)</p> <p><u>Development of facial neuropathy:</u> GK = 6.1% Surgery = 35.3% (<math>p = 0.008</math>)</p>	<p>Study not randomised and significant differences in patient characteristics between groups. Selection bias evident due to different recommended treatment strategies for GK and surgery.</p> <p>Patients known to be lost to follow-up: 24/73 (33%) in GK group. 5/23 (22%) in surgery group.</p> <p>Hearing preservation results not adjusted for multiple comparisons.</p>
(mm)	Surgery	GK																
<20	34.8%	74.0%																
20–39	39.1%	23.3%																
>40	26.1%	2.7%																

KPS:

	GK	Surgery	$p$
Improved	0%	0%	0.796
Unchanged	88%	88%	
Worsened	12%	12%	

Patient satisfaction:

Satisfied with treatment: GK (81.6%) vs surgery (94.1%)  
( $p = 0.216$ )

Recommend to a friend: GK (89.8%) vs surgery (100%)  
( $p = 0.171$ )

Complications:

GK = 4.6%

Surgery = 47.8%

( $p < 0.01$ )

GK: Oedema, hydrocephalus, diplopia imbalance,  
nausea.

Surgery: Oedema, hydrocephalus, diplopia imbalance,  
nausea, CSF leak, seizure, infection, intubation.

Controlled trials—acoustic neuroma						
Level	Author & year	Study design	N	Participant characteristics	Outcomes	Quality
III-3	Regis et al 2002	<p><u>Design:</u> Prosecutive, consecutive cohort with historical control.</p> <p><u>Outcomes:</u> Functional outcomes (facial function, ocular symptoms, eating difficulties, balance, hearing preservation, other complications, quality of life).</p> <p><u>Intervention(s):</u></p> <p>GK: Patients treated by a cobalt-60 201-source Leksell Gamma Knife. Prescribed dose to tumour margin 14 Gy for stage I and small stage II tumours, ≤12 Gy for larger tumours.</p> <p>Surgery: Translabyrinthine surgery performed in 85% of patients and middle fossa approach in 15% when hearing preservation considered feasible.</p> <p><u>Follow-up:</u> GK: 6 months, 1, 2, 3, 5, 7, and 10 years post-GK. Functional evaluation questionnaire completed by patients after more than 3 years post-GK.</p>	<p>N = 207</p> <p>GK = 97</p> <p>Surgery = 110</p>	<p><u>Inclusion:</u> Patients with acoustic neuroma (only unilateral stage II or III tumours with no previous surgical resection) undergoing GK or surgery. GK group treated between July 1992 and June 1998. Surgical group were surviving patients treated between June 1983 and December 1990.</p> <p><u>Exclusion:</u> Neurofibromatosis.</p> <p>Treatment groups matched on tumour size based on inclusion of stage II and III patients only. GK and surgery groups balanced on age, gender, size of populations, and cranial nerve impairment. Preliminary analysis showed no differences in functional outcome between stage II and III patients within treatment groups.</p>	<p><b>Facial function</b></p> <p><u>No facial motor disturbance:</u> GK (100%) vs Surgery (53%) (<math>p = 0.00005</math>)</p> <p><u>Hemifacial spasm:</u> GK (8%) vs Surgery (29%) (<math>p = 0.002</math>)</p> <p><u>Subjective trigeminal symptoms:</u> GK (20%) vs Surgery (55%) (<math>p &lt; 0.0001</math>, chi-square calculated from data in paper)</p> <p><u>Facial sensory disturbance in patients without preoperative trigeminal nerve deficit:</u> GK (4%) vs Surgery (29%) (<math>p = 0.0009</math>)</p> <p><b>Ocular symptoms</b></p> <p><u>No ocular symptoms:</u> GK (49%) vs Surgery (17%) (<math>p &lt; 0.0001</math>, chi-square calculated from data in paper)</p> <p><u>Ocular problems in patients with no postoperative facial palsy:</u> GK (27%) vs Surgery (up to 75%) (<math>p &lt; 0.000001</math>)</p> <p><b>Eating difficulties</b></p> <p><u>Difficulties in chewing:</u> GK (8%) vs Surgery (13%) (<math>p = 0.3</math>, chi-square calculated from data in paper)</p> <p><u>Eating difficulties in absence of clinical injury to V or VII cranial nerves:</u> GK (9%) vs Surgery (28%) (<math>p = 0.004</math>)</p> <p><b>Balance</b></p> <p><u>Pre-treatment balance disturbance cured:</u> GK (47%) vs Surgery (47%) (<math>p = \text{ns}</math>)</p> <p><u>New balance disturbance after treatment:</u> GK (26%) vs Surgery (22%) (<math>p = \text{ns}</math>).</p> <p><b>Hearing</b></p> <p><u>Functional hearing preservation:</u> GK (40%) vs Surgery (5%) (<math>p = 0.000001</math>). However, hearing preservation achieved in 4/11 (45%) surgical patients for whom it was attempted (<math>p = 0.76</math>, Fisher's exact calculated from data in paper)</p>	<p>Study not randomised.</p> <p>Comparison to historical surgical group problematic given advances in surgery since 1983.</p> <p>Follow-up of surgical patients is not described.</p> <p>Cannot determine validation of functional outcomes questionnaire.</p> <p>Questionnaire presented is translated from French, and there may be interpretative difficulties (eg, questionnaire asks about 'swallowing' whereas discussion refers to problems in 'chewing').</p> <p>QoL not measured with a recognised instrument.</p> <p>Recall bias possible in answering questionnaire.</p>

**Complications**

*Mortality:* No deaths linked to GK. Surgery-related mortality rate of 1%.

*Other complications:* GK: Hydrocephalus, no pain reported. Surgery: SCF leakage, haematomas, brain trauma, meningitis, 66% reported some pain.

**QoL**

*No change in daily life:* GK (91%) vs Surgery (61%) ( $p = 0.00017$ )

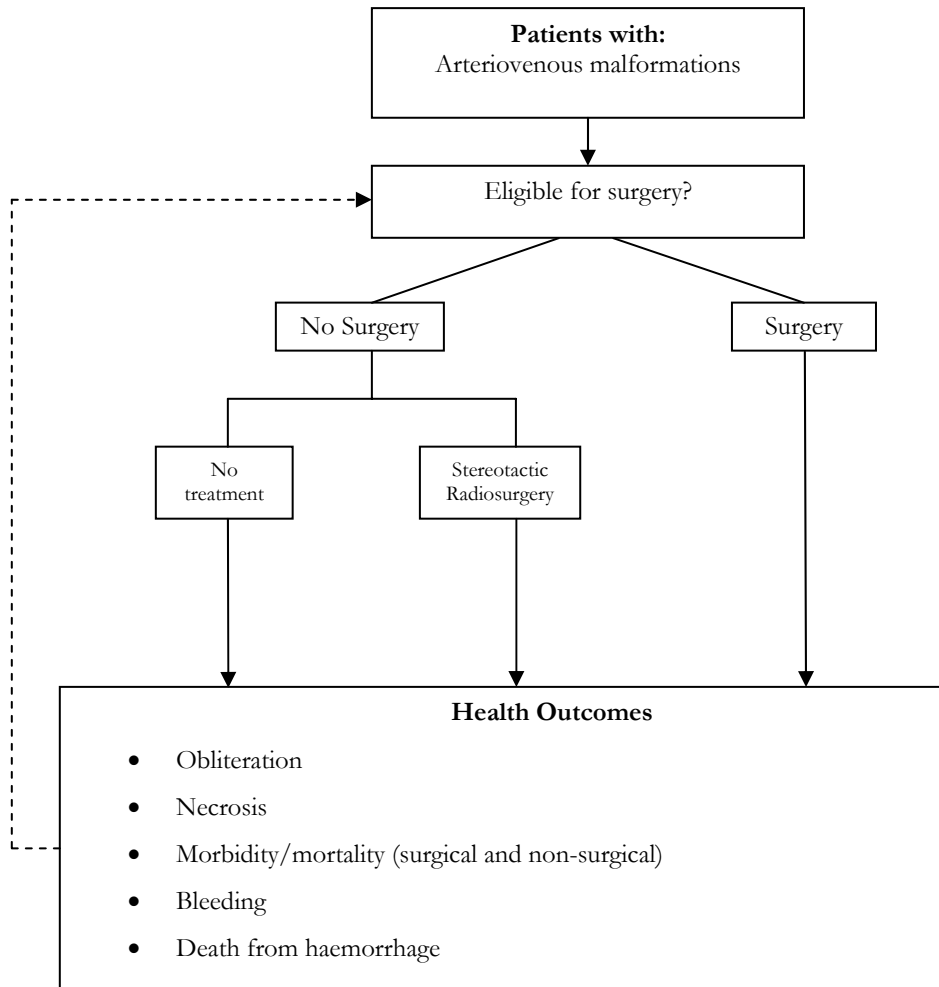
*Psychobehavioural problems:* GK (24%) vs Surgery (69%) ( $p = 0.000001$ )

*Return to previous occupation:* GK (99%) vs Surgery (66%) ( $p = 0.00016$ )

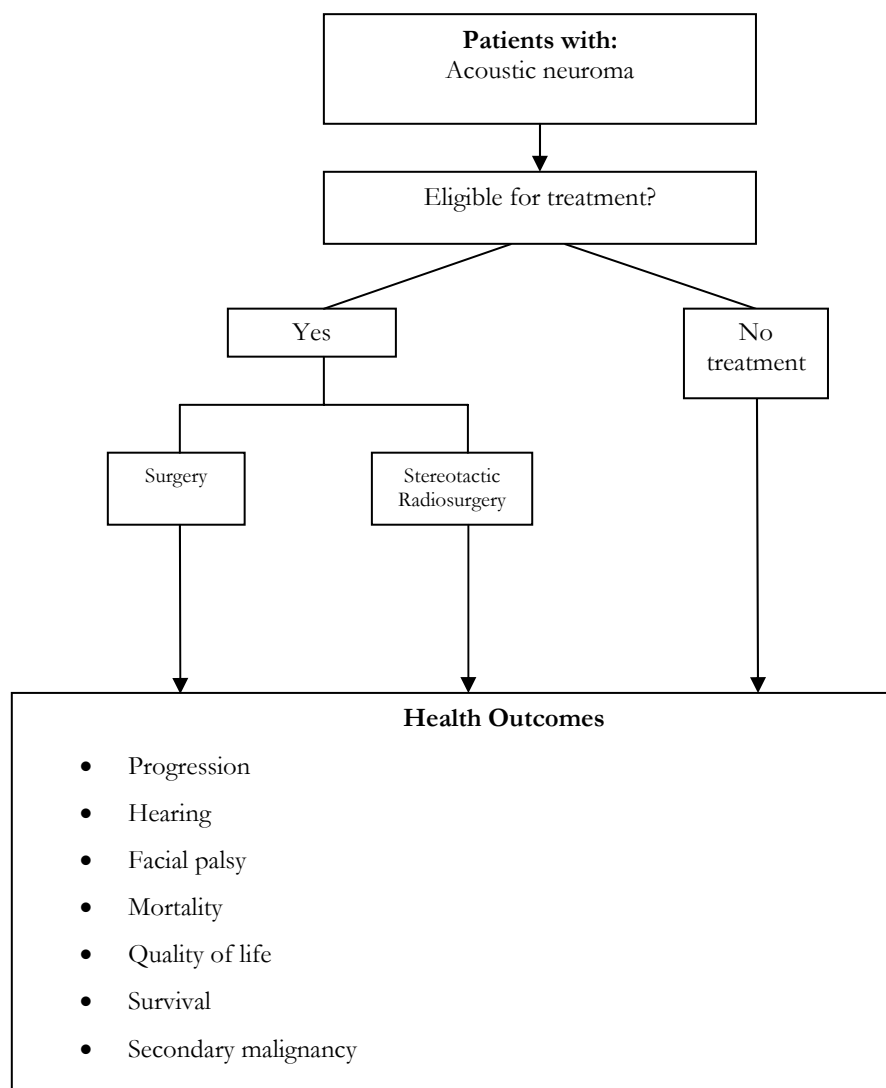
Abbreviations: AVM = arteriovenous malformation; BCNU = a proprietary form of the drug carmustine; EBRT = external-beam radiotherapy; FSRT = fractionated stereotactic radiotherapy; GH = growth hormone; GK = Gamma Knife radiosurgery; HSV = herpes simplex virus; ITT = intention to treat; KPS = Karnofsky Performance Score; Linac = linear accelerator radiosurgery; MAS = Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario; MMSE = Mini Mental Status Examination; NF2 = neurofibromatosis type 2; nr = not reported; ns = not significant; NSCLC = Non-small Cell Lung Cancer; QoL = quality of life; RCT = randomised controlled trial; SRS = stereotactic radiosurgery; Sx = surgery; VS = vestibular schwannoma; WBRT = whole-brain radiotherapy.



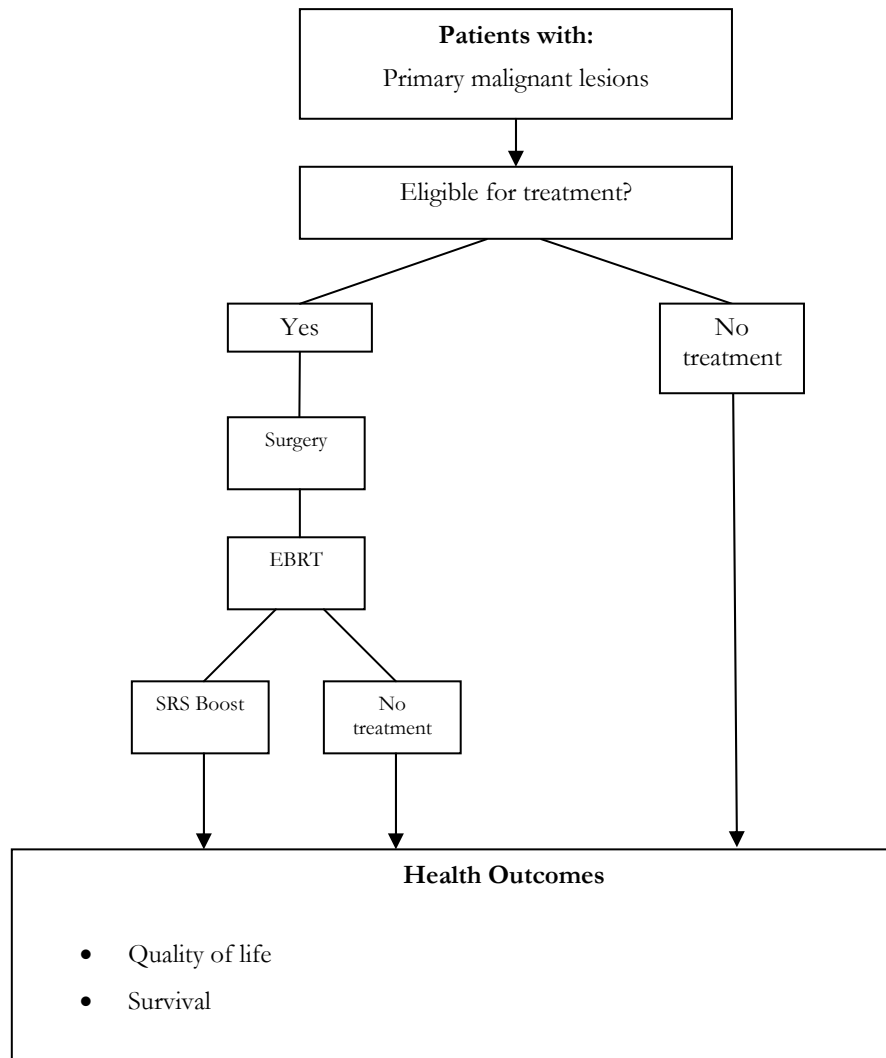
## Arteriovenous malformations



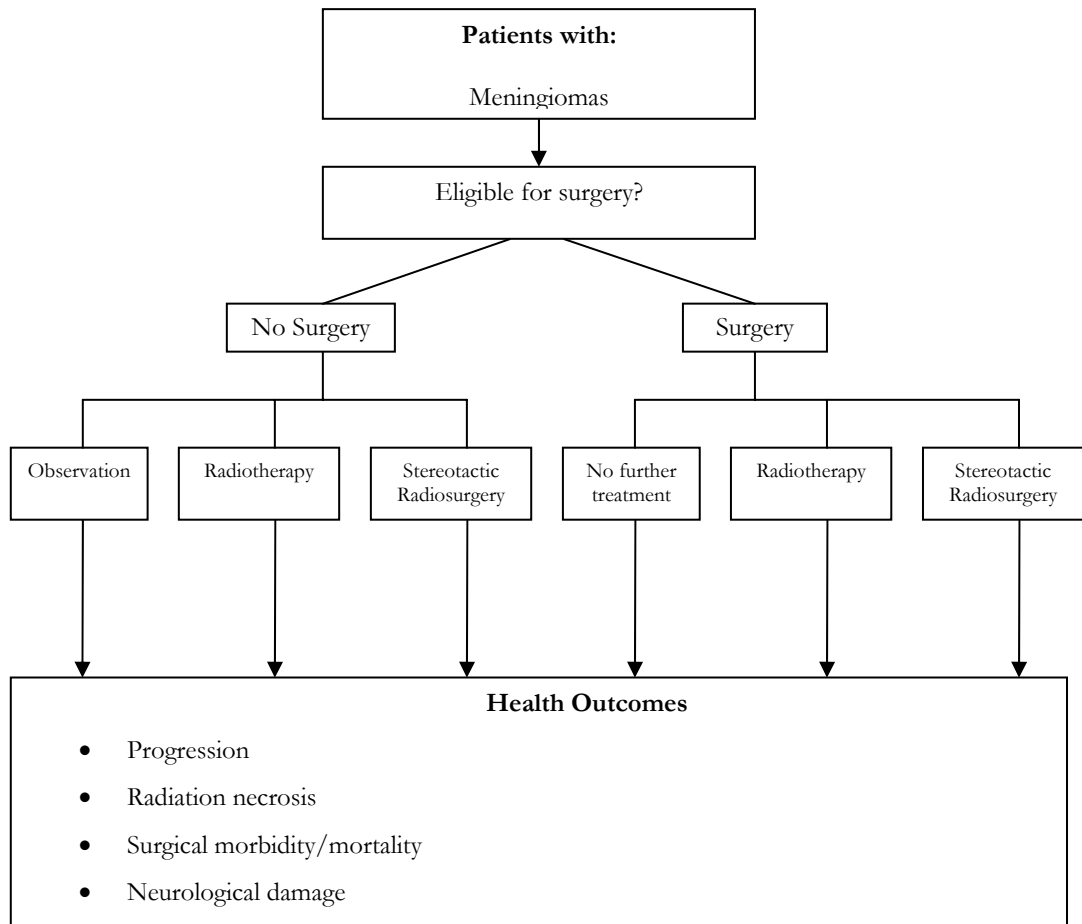
## Acoustic neuroma



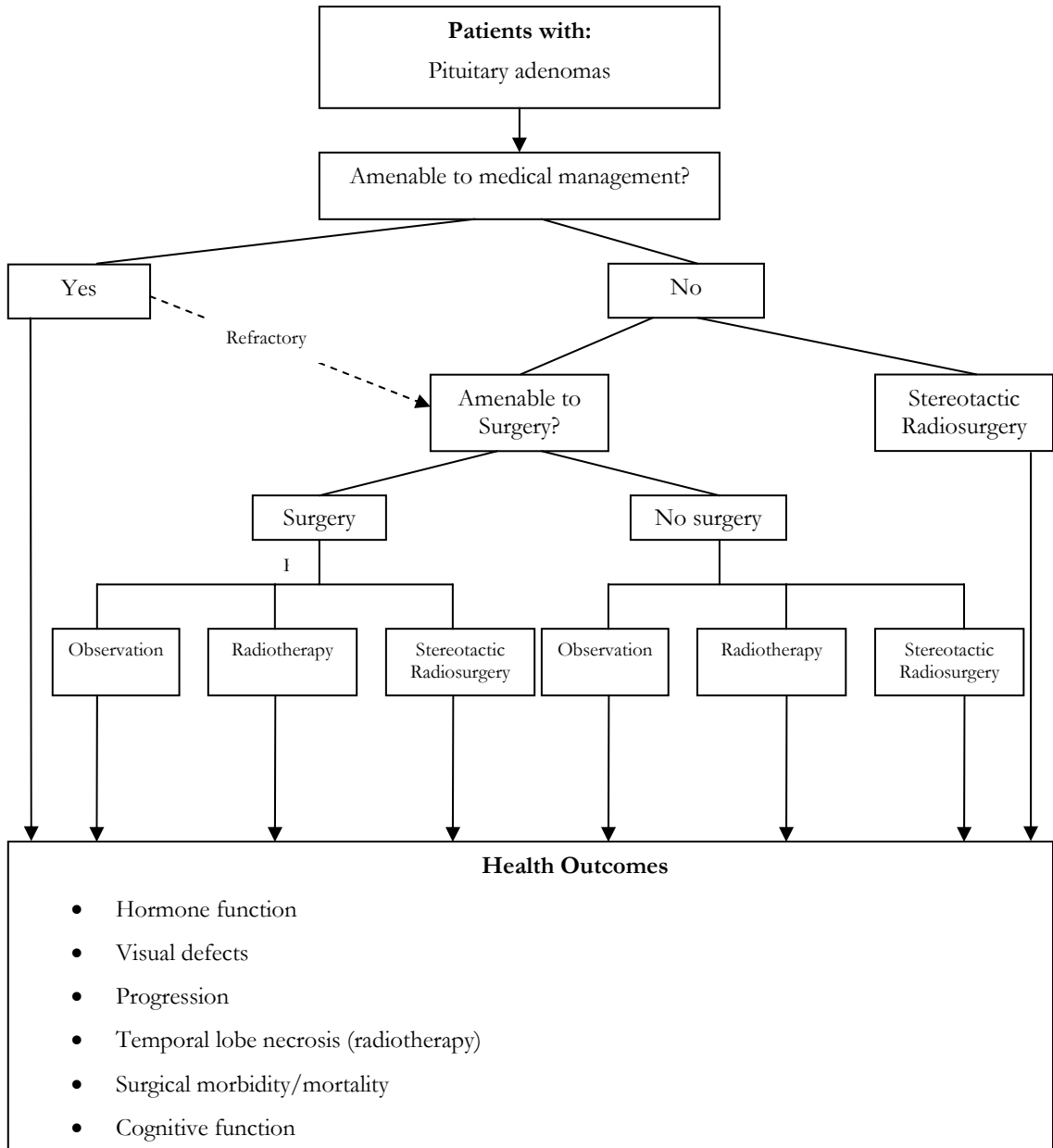
## Primary malignant lesions



## Meningioma



## Pituitary adenoma



# Abbreviations

---

AACR	Australian Association of Cancer Registries
AETMIS	Agence d'évaluation des technologies et des modes d'intervention en sante
AIHW	Australian Institute of Health and Welfare
ASTRO	American Society for Therapeutic Radiology and Oncology
AVM	arteriovenous malformation
BCNU	a proprietary form of the drug carmustine
CSF	cerebrospinal fluid
CT	computed tomography
CTC	Clinical Trials Centre
DARE	Database of Abstracts of Review of Effectiveness
EBRT	external-beam radiotherapy
EORTC	European Organisation for Research in the Treatment of Cancer
GH	growth hormone
GK	Gamma Knife radiosurgery
HTA	health technology assessment
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
KPS	Karnofsky Performance Score
Linac	linear accelerator
MAS	Medical Advisory Secretariat of the Ministry of Health and Long-Term Care, Ontario
MBS	Medical Benefits Schedule
MMSE	Mini Mental Status Examination
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council

NIH	National Institutes of Health
OR	odds ratio
QoL	quality of life
RCT	randomised controlled trial
RPA	recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group
SRS	stereotactic radiosurgery
UK	United Kingdom
USA	United States of America
WBRT	whole-brain radiotherapy

## References

---

- Accuray 2005. *CyberKnife radiosurgery system*, Accuray Incorporated, Sunnyvale, California.
- AETMIS 2004. *Gamma Knife and linear accelerator stereotactic radiosurgery*, Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Montreal.
- AIHW 2004. *Cancer in Australia 2001*, Australian Institute of Health and Welfare (AIHW), Canberra.
- AIHW 2005a *National Hospital Morbidity Database: Principal Diagnosis Data Cubes*. [Internet] Australian Institute of Health and Welfare (AIHW). Canberra. Available from: <http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/principaldiagnosis9899-0405> [Accessed 3 November 2005]
- AIHW 2005b *National Hospital Morbidity Database: Procedures Data Cubes*. [Internet] Australian Institute of Health and Welfare (AIHW). Canberra. Available from: [http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/procedures\\_02030304](http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/procedures_02030304) [Accessed 3 November 2005]
- Andrews, D.W., Scott, C.B., Sperduto, P.W., Flanders, A.E., Gaspar, L.E., Schell, M.C., Werner-Wasik, M., Demas, W., Ryu, J., Bahary, J.P., Souhami, L., Rotman, M., Mehta, M.P., & Curran, W.J., Jr. 2004. 'Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial', *Lancet*, 363 (9422), 1665–1672.
- Australian Government Department of Health and Ageing, 2004. *Medicare Benefits Schedule Book: Operating from November 1 2004*, Commonwealth of Australia, Canberra.
- AVM Study Group 1999. 'Current concepts: Arteriovenous malformations of the brain in adults', *New England Journal of Medicine*, 340 (23), 1812–1818.
- Barton, M., Frommer, M., & Sam Gabriel, G. 2004, *Overview of cancer services in New South Wales*, Collaboration for Cancer Outcomes Research and Evaluation, South Western Sydney Area Health Service, Sydney.
- Becker, G., Kortmann, R.D., & Bamberg, M. 1998. 'Cost comparison of gamma knife versus linac based radiosurgery', *Radiotherapy & Oncology*, 48 [Suppl 1], 130.
- Bertalanffy, A., Roessler, K., Dietrich, W., Aichholzer, M., Prayer, D., Ertl, A., & Kitz, K. 2001. 'Gamma knife radiosurgery of recurrent central neurocytomas: A preliminary report', *Journal of Neurology, Neurosurgery & Psychiatry*, 70 (4), 489–493.
- Black, P.M. 1995. 'Benign brain tumors. Meningiomas, pituitary tumors, and acoustic neuromas', *Neurologic Clinics*, 13 (4), 927–952.
- Black, P.M. & Johnson, M.D. 2004. 'Surgical resection for patients with solid brain metastases: current status', *Journal of Neuro-Oncology*, 69 (1–3), 119–124.

- Brown, P.D., Brown, C.A., Pollock, B.E., Gorman, D.A., & Foote, R.L. 2002. 'Stereotactic radiosurgery for patients with "radioresistant" brain metastases', *Neurosurgery*, 51 (3), 656–665.
- Brown, R.D.J. & Wiebers, D.O. 1988. 'Natural history of unrupture intracranial arteriovenous malformations', *Journal of Neurosurgery*, 68, 352–357.
- Choi, J.H. & Mohr, J.P. 2005. 'Brain arteriovenous malformations in adults', *Lancet Neurology*, 4 (5), 299–308.
- Clayton, R.N. 1999. 'Sporadic pituitary tumours: From epidemiology to use of databases', *Best Practice & Research Clinical Endocrinology & Metabolism*, 13 (3), 451–460.
- Commonwealth Department of Health and Ageing 2002, *Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee: Including major submissions involving economic analyses*, Commonwealth of Australia, Canberra.
- Elekta Instruments 2000, Elekta Instruments web page [Internet]. Available from <http://www.elekta.com>. [Accessed 10 October 2005].
- Ezzat, S., Asa, S.L., Couldwell, W.T., Barr, C.E., Dodge, W.E., Vance, M.L., & McCutcheon, I.E. 2004. 'Prevalence of pituitary adenomas: A systematic review', *Cancer*, 101 (3), 613–619.
- Glasscock, M.E., Hart, M.J., & Vrabec, J.T. 1992. 'Management of bilateral acoustic neuroma', *Otolaryngologic Clinics of North America*, 25 (2), 449–469.
- Hailey, D. 2002, *Stereotactic radiosurgery: An update*, Alberta Heritage Foundation for Medical Research, Edmonton, Alberta.
- Hamilton, M.G. & Spetzler, R.F. 1994. 'Prospective application of a grading system for arteriovenous malformations', *Neurosurgery*, 34, 2–6.
- Hart, D.J. & Giannotta, S.L. 2003. 'Complex cranial base meningioma: Combined management', *Techniques in Neurosurgery*, 9 (2), 86–92.
- Hart, M.G., Grant, R., Walker, M., & Dickinson H. 2004. 'Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases', *Cochrane Database of Systematic Reviews 2004* (Issue 4).
- Horton, J., Baxter, D.H., & Olson, K.B. 1971. 'Management of metastases to the brain by irradiation and corticosteroids', *American Journal of Roentgenology, Radium Therapy & Nuclear Medicine*, 111 (2), 334–336.
- Ikeda, H., Jokura, H., & Yoshimoto, T. 2001. 'Transsphenoidal surgery and adjuvant gamma knife treatment for growth hormone-secreting pituitary adenoma', *Journal of Neurosurgery*, 95 (2), 285–291.
- Karim, A.B., Afra, D., Cornu, P., Bleehan, N., Schraub, S., De Witte, O., Darcel, F., Stenning, S., Pierart, M., & Van Glabbeke, M. 2002. 'Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study

BRO4: An interim analysis', *International Journal of Radiation Oncology, Biology, Physics*, 52 (2), 316–324.

Karpinos, M., Teh, B.S., Zeck, O., Carpenter, L.S., Phan, C., Mai, W.Y., Lu, H.H., Chiu, J.K., Butler, E.B., Gormley, W.B., & Woo, S.Y. 2002. 'Treatment of acoustic neuroma: stereotactic radiosurgery vs. microsurgery', *International Journal of Radiation Oncology, Biology, Physics*, 54 (5), 1410–1421.

Khan, K., ter Riet, G., Popay, J., Glanville, J., Sowden, A., & Kleijnen, J. 2001, 'Study quality assessment'. In *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*, 2nd edn, K. Khan et al, eds., NHS Centre for Research and Dissemination, York, pp. 1–20.

Kondziolka, D., Patel, A., Lunsford, L.D., Kassam, A., & Flickinger, J.C. 1999. 'Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases', *International Journal of Radiation Oncology, Biology, Physics*, 45 (2), 427–434.

Konigsmaier, H., de PauliFerch, B., Hackl, A., & Pendl, G. 1998. 'Costs of radiosurgical treatment: comparison between gamma knife and linear accelerator', *Acta Neurochirurgica*, 140 (11), 1101–1110; discussion 1110–1111.

Kurtz, J.M., Gelber, R., Brady, L.W., Carella, R.J., & Cooper, J.S. 1981. 'Palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group', *International Journal of Radiation Oncology, Biology, Physics*, 7 (7), 891–895.

Lang, F.F. & Sawaya, R. 1998. 'Surgical treatment of metastatic brain tumors', *Seminars in Surgical Oncology*, 14 (1), 53-63.

Laperriere, N., Perry, J., & Zuraw, L. 2004, *Radiotherapy for newly diagnosed malignant glioma in adults*, Practice guideline report; no. 9-3, Cancer Care Ontario, Toronto.

Lawton, M.T. & UCSF Brain Arteriovenous Malformation Study Project. 2003. 'Spetzler–Martin Grade III arteriovenous malformations: surgical results and a modification of the grading scale', *Neurosurgery*, 52 (4), 740–748.

Levin, V.A., Leibel, S.A., & Gutin, P.H. 2001, 'Neoplasms of the central nervous system.' In *Cancer: Principles and Practice of Oncology*, 6th edn, V. T. J. DeVita, S. Hellman, & S. A. Rosenberg, eds., Lippincott Williams & Wilkins, Philadelphia, pp. 2100-2160.

Lin, D., Hegarty, J.L., Fischbein, N.J., & Jackler, R.K. 2005. 'Prevalence of "incidental" acoustic neuroma', *Archives of Otolaryngology—Head & Neck Surgery*, 131 (3), 241–244.

Lindquist, C. 1995. 'Gamma Knife radiosurgery', *Seminars in Radiation Oncology*, 5 (3), 197–202.

Linskey, M.E., Davis, S.A., & Ratanatharathorn, V. 2005. 'Relative roles of microsurgery and stereotactic radiosurgery for the treatment of patients with cranial meningiomas: A single-surgeon 4-year integrated experience with both modalities', *Journal of Neurosurgery*, 102 Suppl, 59–70.

- Lusis, E. & Gutmann, D.H. 2004. 'Meningioma: An update', *Current Opinion in Neurology*, 17 (6), 687–692.
- Markesbery, W.R., Brooks, W.H., Gupta, G.D., & Young, A.B. 1978. 'Treatment for patients with cerebral metastases', *Archives of Neurology*, 35 (11), 754–756.
- MAS 2002, *Gamma Knife*, Medical Advisory Secretariat, Ministry of Health and Long-Term Care, Toronto.
- Mast, H., Young, W.L., Koennecke, H.-H., Sciacca, R.R., Osipov, A., Pile-Spellman, J., Haccin-Bey, L., Duong, H., Stein, B.M., & Mohr, J.P. 1997. 'Risk of spontaneous hemorrhage after diagnosis of cerebral arteriovenous malformation', *Lancet*, 350 (9084), 1065–1068.
- Mehta, M.P., Tsao, M.N., Whelan, T.J., Morris, D.E., Hayman, J.A., Flickinger, J.C., Mills, M., Rogers, C.L., & Souhami, L. 2005. 'American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases', *International Journal of Radiation Oncology Biology Physics*, 63 (1), 37–46.
- Mintz, A.P., Kestle, J.R., Rathbone, M.P., Gaspar, L., Hugenholtz, H., Fisher, B., Duncan, G., Skingley, P., Foster, G., & Levine, M. 1996. 'Randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis', *Cancer*, 78 (7), 1470–1476.
- Mitchell, A.W. 2001, *Stereotactic radiosurgery for brain tumours and arteriovenous malformations*, vol. 1, no. 13, Wessex Institute for Health Research & Development, Southampton.
- Mor, V., Laliberte, L., Morris, J.N., & Wiemann, M. 1984. 'Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting', *Cancer*, 53 (9), 2002–2007.
- MSAC 2001, *Gamma knife radiosurgery*, Medical Services Advisory Committee, Commonwealth of Australia, Canberra.
- Muacevic, A., Kreth, F.W., Horstmann, G.A., SchmidElsaesser, R., Wowra, B., Steiger, H.J., & Reulen, H.J. 1999. 'Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter', *Journal of Neurosurgery*, 91 (1), 35–43.
- Myrseth, E., Moller, P., Pedersen, P.-H., Vassbotn, F.S., Wentzel-Larsen, T., & Lund-Johansen, M. 2005. 'Vestibular schwannomas: Clinical results and quality of life after microsurgery or gamma knife radiosurgery', *Neurosurgery*, 56 (5), 927–934.
- Nakamura, M., Roser, F., Michel, J., Jacobs, C., & Samii, M. 2003. 'Natural history of incidental meningiomas', *Neurosurgery*, 53 (1), 62–70; discussion 70–71.
- NHMRC 2000. *How to review the evidence: systematic identification and review of the scientific literature*, National Health and Medical Research Council, Commonwealth of Australia, Canberra.
- NIH Consensus Development Panel 1991. *Acoustic Neuroma. NIH Consensus Statement Online* [Internet]. National Institutes of Health, Dec 11–13. NIH Online 9 (4), 1–24.

Available from: <http://consensus.nih.gov/1991/1991AcousticNeuroma087html.htm> [Accessed 11 October 2005].

NIH 2005 *Childhood Brain Tumors (PDQ®): Treatment*. [Internet] National Institutes of Health (NIH). Bethesda, Maryland. Available from: <http://www.nci.nih.gov/cancertopics/pdq/treatment/childbrain/HealthProfessional> [Accessed 3 November 2005]

NSW Health 2005, *2004 Radiotherapy Management Information Systems Report*, NSW Health Department, Sydney.

OECD 2005, 2003 Purchase Parity Rates [Internet]. Organisation for Economic Co-operation and Development, Paris. Available from: <http://www.oecd.org/dataoecd/61/54/18598754.pdf> [Accessed 17 February 2005].

Ogilvy, C.S., Stieg, P.E., Awad, I., Brown, R.D., Jr., Kondziolka, D., Rosenwasser, R., Young, W.L., Hademenos, G., & Special Writing Group of the Stroke Council, ASA 2001. 'AHA scientific statement: recommendations for the management of intracranial arteriovenous malformations: Statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association', *Stroke*, 32 (6), 1458–1471.

Ohinmaa, A. 2003, *Cost estimation of stereotactic radiosurgery: Application to Alberta*, Alberta Heritage Foundation for Medical Research, Edmonton.

Ondra, S.L., Troupp, H., George, E.D., & Schwab, K. 1990. 'Natural history of symptomatic arteriovenous malformations of the brain: 24 year follow up assessment', *Journal of Neurosurgery*, 73, 387–392.

Ott, K. 1996. 'Comparison of craniotomy and Gamma Knife charges in a community-based Gamma Knife Center', *Stereotactic & Functional Neurosurgery*, 66 Suppl, 1, 357–364.

Patchell, R.A. 1991. 'Brain metastases', *Neurologic Clinics*, 9 (4), 817–824.

Patchell, R.A. 2003. 'Management of brain metastases', *Cancer Treatment Reviews*, 29 (6), 533–540.

Patchell, R.A., Tibbs, P.A., Regine, W.F., Dempsey, R.J., Mohiuddin, M., Kryscio, R.J., Markesbery, W.R., Foon, K.A., & Young, B. 1998. 'Post operative radiotherapy in the treatment of a single metastases to the brain: a randomized trial', *Journal of the American Medical Association*, 280 (17), 1485–1489.

Patchell, R.A., Tibbs, P.A., Walsh, J.W., Dempsey, R.J., Maruyama, Y., Kryscio, R.J., Markesbery, W.R., Macdonald, J.S., & Young, B. 1990. 'Randomized trial of surgery in the treatment of single metastases to the brain', *New England Journal of Medicine*, 322 (8), 494–500.

Petrovich, Z., Yu, C., Giannotta, S.L., O'Day, S., & Apuzzo, M.L. 2002. 'Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery', *Journal of Neurosurgery*, 97 (5 Suppl), 499–506.

- Picozzi, P., Losa, M., Mortini, P., Valle, M.A., Franzin, A., Attuati, L., Ferrari, d.P., & Giovanelli, M. 2005. 'Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas', *Journal of Neurosurgery*, 102 Suppl, 71–74.
- Pollock, B.E., Flickinger, J.C., Lunsford, L.D., Bissonette, D.J. and Kondziolka, D. 1996. 'Factors that predict the bleeding risk of cerebral arteriovenous malformations', *Stroke*, 27, 1–6.
- Pollock, B.E. & Flickinger, J.C. 2002. 'Proposed radiosurgery-based grading system for arteriovenous malformations', *Journal of Neurosurgery*, 96 (1), 79–85.
- Pollock, B.E., Stafford, S.L., Utter, A., Giannini, C., & Schreiner, S.A. 2003. 'Stereotactic radiosurgery provides equivalent tumor control to Simpson Grade 1 resection for patients with small- to medium-size meningiomas', *International Journal of Radiation Oncology, Biology, Physics*, 55 (4), 1000–1005.
- Radhakrishnan, K., Mokri, B., Parisi, J.E., O'Fallon, W.M., Sunku, J., & Kurland, L.T. 1995. 'Trends in incidence of primary brain tumors in the population of Rochester, Minnesota', *Annals of Neurology*, 37 (1), 67–73.
- Regis, J., Pellet, W., Delsanti, C., Dufour, H., Roche, P.H., Thomassin, J.M., Zanaret, M., & Peragut, J.C. 2002. 'Functional outcome after gamma knife surgery or microsurgery for vestibular schwannomas', *Journal of Neurosurgery*, 97 (5), 1091–1100.
- RTOG 2005. *Cooperative Group Common Toxicity Criteria. Radiation Therapy Oncology Group* [Internet]. Radiation Therapy Oncology Group (RTOG). Philadelphia, PA. Available from: <http://www.rtog.org/members/toxicity/tox.html> [Accessed 27 November 2005].
- RTOG/EORTC. *RTOG/EORTC Late Radiation Morbidity Scoring Schema* [Internet]. Radiation Therapy Oncology Group, Philadelphia. Available from: <http://www.rtog.org/members/toxicity/late.html> [Accessed 26 November 2005].
- Rutigliano, M.J., Lunsford, L.D., Kondziolka, D., Strauss, M.J., Khanna, V., & Green, M. 1995. 'Cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors', *Neurosurgery*, 37 (3), 445–453; discussion 453–455.
- Sagar, S.M. & Israel, M.A. 2004. 'Primary and metastatic tumors of the nervous system'. In *Harrison's principles of internal medicine*, 16th edn, D.L. Kasper et al, eds. McGraw-Hill, New York.
- Sheehan, J.P., Niranjan, A., Sheehan, J.M., Jane, J.A., Jr., Laws, E.R., Kondziolka, D., Flickinger, J., Landolt, A.M., Loeffler, J.S., & Lunsford, L.D. 2005. 'Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium', *Journal of Neurosurgery*, 102 (4), 678–691.
- Smee, R. Anonymous, Jul 17, 2000. Radiosurgery in Australia.
- Solberg, T.D., Selch, M., Smathers, J.B., & De Salles, A.A.F. 1998. 'Fractionated stereotactic radiotherapy: rationale and methods', *Medical Dosimetry*, 23 (3), 209–219.

Souhami, L., Seiferheld, W., Brachman, D., Podgorsak, E.B., Werner-Wasik, M., Lustig, R., Schultz, C.J., Sause, W., Okunieff, P., Buckner, J., Zamorano, L., Mehta, M.P., & Curran, W.J., Jr. 2004. 'Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: Report of Radiation Therapy Oncology Group 93-05 protocol', *International Journal of Radiation Oncology, Biology, Physics*, 60 (3), 853–860.

Spetzler, R.F. & Martin, N.A. 1986. 'Proposed grading system for arteriovenous malformations', *Journal of Neurosurgery*, 65, 476–483.

Stapf, C., Mast, H., Sciacca, R.R., Berenstein, A., Nelson, P.K., Gobin, Y.P., PileSpellman, J., Mohr, J.P., & New York Islands AVM Study Collaborators 2003. 'New York Islands AVM Study: Design, study progress, and initial results', *Stroke*, 34 (5), e29–33.

Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., Belanger, K., Brandes, A.A., Marosi, C., Bogdahn, U., Curschmann, J., Janzer, R.C., Ludwin, S.K., Gorlia, T., Allgeier, A., Lacombe, D., Cairncross, J.G., Eisenhauer, E., Mirimanoff, R.O., European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups & National Cancer Institute of Canada Clinical Trials Group 2005. 'Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma', *New England Journal of Medicine*, 352 (10), 987–996.

Tomasevic, P., Hook, C., & Smee, R. 1998. 'Stereotactic radiosurgery as a treatment option for selected acoustic neuroma patients', *Australian Journal of Otolaryngology*, 3 (1), 7–11.

Tos, M., Stangerup, S.E., CayeThomasen, P., Tos, T., & Thomsen, J. 2004. 'What is the real incidence of vestibular schwannoma?', *Archives of Otolaryngology—Head & Neck Surgery*, 130 (2), 216–220.

Tsao, M.N., Lloyd, N.S., Wong, R.K., Rakovitch, E., Chow, E., Laperriere, N., & Supportive Care Guidelines Group of Cancer Care Ontario's Program in Evidence-based Care 2005a. 'Radiotherapeutic management of brain metastases: Systematic review and meta-analysis', *Cancer Treatment Reviews*, 31 (4), 256–273.

Tsao, M.N., Mehta, M.P., Whelan, T.J., Morris, D.E., Hayman, J.A., Flickinger, J.C., Mills, M., Rogers, C.L., & Souhami, L. 2005b. 'American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma', *International Journal of Radiation Oncology, Biology, Physics*, 63 (1), 47–55.

UCSF Acoustic Neuroma Team 1998. *UCSF Information on Acoustic Neuroma* [Internet]. University of California San Francisco. San Francisco, CA. Available from: <http://itsa.ucsf.edu/~rkj/IndexAN.html> [Accessed 1 September 2005].

Valavanis, A. & Yasargil, M.G. 1998. 'Endovascular treatment of brain arteriovenous malformations', *Advances & technical standards in neurosurgery*, 24, 131–214.

van Roijen, L., Nijs, H.G., Avezaat, C.J., Karlsson, G., Linqvist, C., Pauw, K.H., & Rutten, F.F. 1997. 'Costs and effects of microsurgery versus radiosurgery in treating acoustic neuroma', *Acta Neurochirurgica*, 139 (10), 942–948.

- Varlotto, J.M., Shrieve, D.C., Alexander, E., Kooy, H.M., Black, P.M., & Loeffler, J.S. 1996. 'Fractionated stereotactic radiotherapy for the treatment of acoustic neuromas: preliminary results', *International Journal of Radiation Oncology, Biology, Physics*, 36 (1), 141–145.
- Vecht, C. J., Haaxma-Reiche, H., Noordijk, E. M., Padberg, G. W., Voormolen, J. H., Hoekstra, F. H., Tans, J. T., Lambooi, N., Metsaars, J. A., & Wattendorff, A. R. 1993. 'Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery?', *Annals of Neurology*, 33 (6), 583–90.
- Weissman, D.E. 1988. 'Glucocorticoid treatment for brain metastases and epidural spinal cord compression: A review', *Journal of Clinical Oncology*, 6, 543–550.
- Wellis, G., Nagel, R., Vollmar, C., & Steiger, H.J. 2003. 'Direct costs of microsurgical management of radiosurgically amenable intracranial pathology in Germany: Analysis of meningiomas, acoustic neuromas, metastases and arteriovenous malformations of less than 3 cm in diameter', *Acta Neurochirurgica*, 145 (4), 249–255.
- Westphal, M., Heese, O., & de Wit, M. 2003. 'Intracranial metastases: therapeutic options', *Annals of Oncology*, 14, 4–10.
- Wilkins, R.H. 1985. 'Natural history of intracranial vascular malformations. A review', *Neurosurgery*, 16, 421–430.
- Yamakami, I., Uchino, Y., Kobayashi, E., & Yamaura, A. 2003. 'Conservative management, gamma-knife radiosurgery, and microsurgery for acoustic neurinomas: Systematic review of outcome and risk of three therapeutic options', *Neurological Research*, 25 (7), 682–690.
- Zimm, S., Wampler, G.L., Stablein, D., Hazra, T., & Young, H.F. 1981. 'Intracerebral metastases in solid-tumor patients: natural history and results of treatment', *Cancer*, 48 (2), 384–394.