Gamma knife radiosurgery

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Assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care 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.

This report was prepared by the Medicare Services Advisory Committee (MSAC) with the assistance of Kirsten Howard, Epidemiologist and Dr Martin Stockler, Senior Lecturer from The NHMRC Clinical Trials Centre, University of Sydney. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 8 August 2001.

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

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Gamma knife radiosurgery is one method of performing radiosurgery, and uses 201 fixed, highly collimated ^{60}Co sources distributed on a sphere and aimed at the target point.

Gamma knife surgery is reported to be a four step procedure: 1) application of the stereotactic frame, 2) image acquisition, 3) dose planning and 4) radiation delivery (Lindquist 1995; Elekta Instruments 2000). An appropriate 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 target coordinate determination and is used to immobilise and position the patient's head within the collimator helmet during treatment. Stereotactic image acquisition is the basis of dose planning and images are usually generated by angiography, computerised 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. The actual radiation delivery occurs when the patients is placed on the 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 ^{60}Co beams. The bed moves into the Gamma Unit to initiate treatment, with a typical treatment session lasting approximately 40–60 minutes, depending on the complexity of the treatment plan. The bed moves out of the Gamma Unit at the end of treatment (Lindquist 1995; Elekta Instruments 2000).

Medicare Services Advisory Committee – role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care 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 the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the National Health and Medical

Research Council (NHMRC) Clinical Trials Centre, University of Sydney, was engaged to conduct a systematic review of literature on gamma knife radiosurgery. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of gamma knife radiosurgery

The poor methodological quality of published data precludes any definitive assessment of the safety and efficacy of gamma knife radiosurgery as a treatment option for arteriovenous malformations, cerebral metastases and acoustic neuroma. Due to differences in the characteristics of patients treated, it is not possible to determine whether radiosurgery treatment is superior to treatment with conventional methods (eg surgery). There is also insufficient information to determine conclusively whether one method of radiosurgery is superior to another.

Safety

There is insufficient evidence available to provide a comprehensive assessment of the safety of gamma knife radiosurgery and its comparators. Methodological limitations and patient heterogeneity limits the generalisability of uncontrolled evidence. In no indication was it possible to determine whether one method of radiosurgery was safer than another.

Arteriovenous malformations

Microsurgical excision of arteriovenous malformations results in permanent neurological complication rates of up to 15 per cent. This decreases to less than 5 per cent in patients with small, easily accessible lesions.

Permanent neurological complications occurred in 1–10 per cent of patients treated with radiosurgery.

Cerebral metastases

Little safety information is available from the single, small randomised trial.

Uncontrolled case series suggested that acute radiation-induced oedema developed in up to 20 per cent of patients treated with radiosurgery. Suspected or confirmed radiation necrosis developed as a significant or long-term complication in up to 10 per cent of patients; 6 per cent required intervention for symptomatic radiation necrosis and in 1 per cent of patients the radiation necrosis was fatal.

Acoustic neuroma

Microsurgical excision results in facial nerve complication rates of up to 20 per cent at one year and useful hearing preservation rates of between approximately 30 per cent and 90 per cent.

Radiosurgical treatment results in facial nerve complications and useful hearing preservation rates similar to microsurgery.

Limited information was available on other procedural complications.

Effectiveness

There is insufficient evidence to provide a comprehensive assessment of the effectiveness of gamma knife radiosurgery and its comparators. Methodological limitations and patient heterogeneity limit the generalisability of uncontrolled evidence. In no indication was it possible to determine whether one method of radiosurgery was superior to another.

Arteriovenous malformations

Patients treated with microsurgery achieve complete excision rates of 85–100 per cent. This increases to 94–100 per cent for patients with small, easily accessible lesions.

Literature reported obliteration rates for radiosurgery are likely to be an overestimation of the true rate of arteriovenous malformation (AVM) obliteration due to 1) inadequate patient follow-up and 2) only a proportion of patients eligible for angiography at any given time point actually undergoing the procedure.

Two-year obliteration rates (when reported as a percentage of those patients eligible for angiography) range from 26–45 per cent for gamma knife radiosurgery and 44–68 per cent for linear accelerator (LINAC) radiosurgery.

Cerebral metastases

The single, small randomised trial suggests there may be slightly improved local control for patients treated with radiosurgery plus whole brain radiotherapy (WBRT) compared to WBRT alone. There was, however, no survival benefit for these patients.

The results of uncontrolled case series generally supported those of the randomised trial.

Acoustic neuroma

Microsurgical excision results in complete excision rates of close to 100 per cent (in patients particularly selected for surgery).

Radiosurgical treatment results in tumour control rates (ie stability or regression of tumour) of between 80 per cent and 100 per cent.

Cost-effectiveness

As the issues of effectiveness and safety are yet to be conclusively determined, it is not possible to perform a true economic evaluation of the role of gamma knife radiosurgery or comparators in managing patients with arteriovenous malformations, brain metastases and acoustic neuroma.

Cost estimates suggest that the ratio of gamma knife equipment cost per treatment to LINAC equipment cost per treatment is 1.7–2.9 over a range of possible scenarios. i.e. gamma knife was 1.7 to 2.9 times more expensive than LINAC, depending on the costing scenario examined.

Overall

Overall, microsurgical resection remains an acceptable therapeutic intervention, particularly for patients with small, easily accessible arteriovenous malformations and acoustic neuromas.

Radiosurgery may be an effective treatment for selected groups of patients with arteriovenous malformations and acoustic neuroma, for example those patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention.

Outcomes for patients with cerebral metastases are likely to be influenced more by baseline prognostic factors than the type of treatment.

Evidence does not indicate a difference in outcomes for patients treated with gamma knife or LINAC radiosurgery.

Recommendation

Since there is currently insufficient evidence on comparative safety, effectiveness and cost-effectiveness pertaining to gamma knife radiosurgery, MSAC recommended that additional public funding should not be supported at this time for this procedure.

- The Minister for Health and Aged Care accepted this recommendation on 8 August 2001 -

Introduction

The Medicare Services Advisory Committee (MSAC) has reviewed the use of gamma knife radiosurgery, which is a 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 in the indications of arteriovenous malformations, cerebral metastases and acoustic neuroma.

Background

Gamma knife radiosurgery

This evaluation was undertaken in response to an application for assessment of gamma knife radiosurgery, which does not currently have specific reimbursement under the Australian Medicare Benefits Scheme. Stereotactic radiosurgery (that is, LINAC radiosurgery, as all currently operating facilities are modified linear accelerators) is currently eligible for funding under the Australian Medicare Benefits Schedule (Commonwealth Department of Health and Aged Care 1999a).

The concept of stereotactic radiosurgery is based on the stereotactic targeting of intracranial lesions and their treatment by a large single fraction of ionising radiation delivered by multiple collimated (or 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 is due either to direct cell damage or to vascular occlusion.

There are three potential methods for delivering stereotactic irradiation:

- linear accelerator (LINAC),
- gamma knife, and
- charged-particle irradiation.

The LINAC method is an extension of arc radiotherapy, with a number of arcs used to achieve rapid dose fall-off in all directions. The gamma knife uses 201 fixed, highly collimated ^{60}Co sources distributed on a sphere and aimed at the target point. Charged particle irradiation uses only three to five beams, similar to the beam arrangement in conventional radiotherapy, but uses the depth-dose characteristics of charged particle irradiation to achieve highly localised dose distributions (Phillips et al. 1994).

Fractionated stereotactic radiotherapy divides the dose over multiple treatment sessions, as is seen with conventional radiotherapy treatments. Fractionation of a large dose into many smaller doses exploits the inherent differences in cellular repair capacity between late and acute responding cells. The effect is irreparable damage in acute effect tissues and the relative sparing of late effect tissues (Solberg et al. 1998). Fractionated stereotactic radiotherapy couples this biologic advantage with dosimetric advantages of stereotactic small volume irradiation of radiosurgery. Where stereotactic application of radiation was once only possible in a single dose, improvements in immobilisation of patients and repeat fixation has meant that fractionated delivery is now possible with some delivery systems. Although the possibility of fractionated treatment with a gamma knife is being explored, it is generally regarded as a single fraction treatment. Fractionated dosing is considerably more likely to be used with a linear accelerator system, and offers the advantage of being able to treat larger lesions over a number of treatment sessions. It may also be possible to use fractionated dosing to treat lesions located in critical areas of the brain or close to critical structures which were previously considered unsuitable for stereotactic radiosurgery.

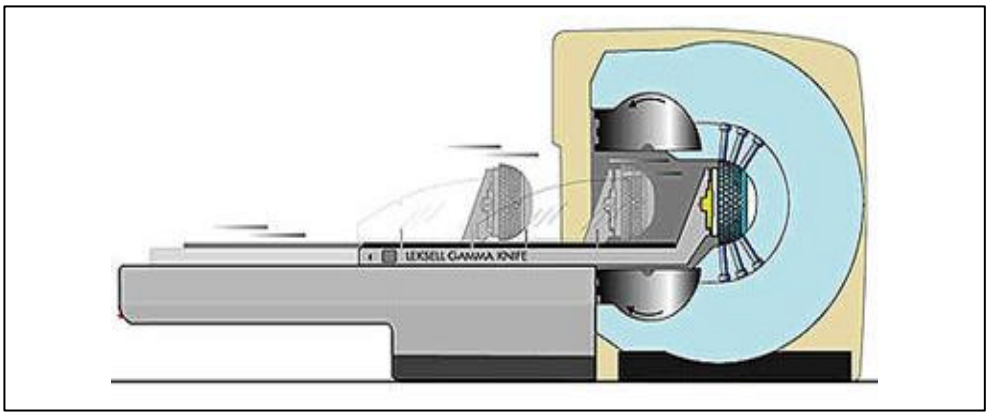
The procedure

Gamma knife radiosurgery is reported to be a four step procedure:

- application of the stereotactic frame,
- image acquisition,
- dose planning, and
- radiation delivery (Lindquist 1995; Elekta Instruments 2000).

An appropriate 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 target coordinate determination and is used to immobilise and position the patient's head within the collimator helmet during treatment. Stereotactic image acquisition is the basis of dose planning and images are usually generated by angiography, CT or 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. The actual radiation delivery occurs when the patient is placed on the 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 ^{60}Co beams. The bed moves into the Gamma Unit to initiate treatment, with a typical treatment session lasts approximately 40–60 minutes, depending on the complexity of the treatment plan. The bed moves out of the Gamma Unit at the end of treatment (Lindquist 1995; Elekta Instruments 2000).

Figure 1 Gamma knife radiosurgery unit



Intended purpose

The applicant has nominated a wide range of clinical indications (over 25) for which gamma knife radiosurgery has been used. The gamma knife is designed to treat intracranial conditions only. The applicant provided additional information for nine of the conditions mentioned in the application. They were:

1. Arteriovenous malformations (AVMs)
2. Acoustic neuroma

3. Meningioma
4. Pituitary tumours
5. Craniopharyngioma
6. Malignant metastases
7. Glial tumours
8. Trigeminal neuralgia
9. Functional disorders

From these nine indications the Supporting Committee decided an initial list of priorities. The indications included were based on likely frequency of treatment and clinical need. These indications included (in decreasing order of priority):

1. Arteriovenous malformations (AVMs)
2. Malignant cerebral metastases
3. Acoustic neuroma
4. High grade glial tumour
5. Pituitary tumour
6. Meningioma
7. Pineal tumour

This initial assessment will review the available evidence for the indications of arteriovenous malformations, malignant cerebral metastases and acoustic neuroma. Extensive additional information about each of these indications is included within the Results of Assessment section of this review.

Clinical need / burden of disease

Brief incidence and prevalence data for the three indications examined in this report are shown in Table 1.

Table 1 Measures of disease burden for selected conditions

Condition	ICD-9-CM code [1]	Hospital separations 1997–98 [2]	Published incidence data	New cases in Australia (per year)
Arteriovenous malformations	74781 – Cerebrovascular anomalies [3]	317	1–10 per 100,000 (Crawford et al. 1986a; Ondra et al. 1990)	190–1,900
Cerebral metastases	1983 – Secondary malignancy (brain/spine) [4]	2987 [5]		
Acoustic neuroma	2251 – Benign neoplasm cranial nerve [6]	371	1 per 100,000 (Nestor et al. 1988; Consensus Development Panel 1994)	190

1 International Classification of Diseases, Clinical Modification, 9th Revision
2 (Commonwealth Department of Health and Aged Care 2000a)
3 Includes all cerebrovascular anomalies, not only AVMs
4 Includes all brain and spine metastases, not only brain
5 This estimate may not be an accurate representation of the true number of patients with cerebral metastases due to coding anomalies whereby some patients with secondary malignancies are coded according to their primary malignancy, rather than the secondary lesion.
6 Includes all benign cranial nerve neoplasms not only acoustic neuroma

Existing procedures and comparators

In this review, gamma knife radiosurgery is compared to a number of alternative treatments or combinations of treatments including surgery, LINAC radiosurgery and radiotherapy. There are currently eight functioning LINAC radiosurgery facilities in Australia, although the frequency with which they perform radiosurgery may vary widely between centres.

Marketing status of the device

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 currently specifically listed in the Medicare Schedule of Benefits (Commonwealth Department of Health and Aged Care 1999a). Stereotactic Radiosurgery is listed on the Medicare Benefits Scheme (MBS) Schedule of Benefits, Item Number 15600, with an associated fee of $1,309.65. Although MBS Item Number 15600 does not specifically indicate only LINAC radiosurgery will be reimbursed, all currently operating facilities in Australia are modified linear accelerators.

Approach to assessment

In undertaking this assessment, the literature available on gamma knife radiosurgery and its comparators was reviewed, and a supporting committee was convened to evaluate the evidence surrounding the procedure and provide expert advice.

The research questions

Before starting a review of the literature, MSAC and the Supporting Committee formulated a number of questions. The initial list of priorities was based on likely frequency of treatment. These indications included:

1. arteriovenous malformations
2. malignant cerebral metastases
3. acoustic neuroma
4. high grade glial tumour
5. pituitary tumour
6. meningioma
7. pineal tumour

The first three will be discussed in this review.

Review of literature

The medical literature was searched to identify relevant studies and reviews. Searches were conducted in the following databases from their commencement until March 2000.

- Medline/Pre-Medline
- HealthSTAR
- Current Contents
- EMBASE
- The Cochrane Library
- ISTAHC Online database (International Society for Technology Assessment in Health Care)
- NHS Centre for Reviews and Dissemination databases
  - DARE (Database of Abstracts and Reviews of Effectiveness)
  - EED (Economic Evaluation Database)
  - HTA (Health Technology Assessment Database)

The following search strategy was used to identify papers in Medline and HealthSTAR. It was applied with disease-specific search terms as applicable for each research question. *(EMBASE retrievals in italics using equivalent search terms).*

1 exp radiosurgery/ or radiosurgery.mp.	2020	*1793*
2 exp stereotaxic techniques/ or stereotactic.mp.	11603	*4387*
3 (linac or linear accelerator).mp.	1565	*1386*
4 gamma knife.mp.	484	*465*
5 or/1–4	12961	*6123*

A broad search using the term 'radiosurgery' was used for the NHS databases.

The AANS and CNS (American Association of Neurological Surgeons and Congress of Neurological Surgeons) Meeting Abstract Archive was also searched using the keyword 'radiosurgery' (http://cnshome.org/abstracts/search.html).

Additionally, the table of contents of the publication *Radiosurgery* (which is not indexed by Medline, Biosis, Current Contents, Embase or HealthSTAR) was searched (http://karger.ch/bookseries/radio/radio.htm#01/).

Electronic searching also included the Internet sites of the following health technology assessment groups and information sources.

Table 2 Health Technology Assessment Organisations

Organisation	Website
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
ECRI(US)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence which is shown in Table 3.

Table 3 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and 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 and post-test.

Source: (National Health and Medical Research Council (NHMRC) 1999)

Results of searches for each indication are presented within the Results of Assessment. With the exception of one trial for cerebral metastases, all studies identified were case series and lacked control groups (NHMRC Level IV evidence).

Results of previous Health Technology Reports which are directly applicable to specific questions are presented in the body of the document. General findings from such reports are documented in Appendix F.

Expert advice

A supporting committee with expertise in neurosurgery and radiation oncology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee 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 three reviews.

Cerebral arteriovenous malformations

Summary of findings

- Poor methodological quality of published data and variability in patient populations preclude any definitive assessment of radiosurgery for treating arteriovenous malformations.
- Patients treated with microsurgery achieve complete excision rates of between 85 per cent and 100 per cent, with permanent neurological complication rates of up to 15 per cent.
- Microsurgery remains an appropriate treatment option for the subset of patients with small, easily accessible AVMs and in these patients complete excision rates are approximately 94–100 per cent, while permanent neurological complication rates decrease to less than 5 per cent.
- Radiosurgical treatment resulted in permanent neurological complications in approximately 2–10 per cent of patients, with little apparent difference in these rates between patients treated with gamma knife and LINAC modalities.
- Obliteration rates reported in the literature for both LINAC and gamma knife radiosurgery appear to be an overestimation of the true obliteration rate. This is due to:
  - inadequate follow-up of patients, and
  - only a percentage of patients eligible for angiography at any given time point actually undergo the procedure to confirm AVM obliteration.
- These methodological weaknesses limit our ability to draw reliable conclusions regarding the place of radiosurgery.
- Two-year obliteration rates (when reported as a percentage of those patients eligible for angiography) for LINAC are between 44 per cent and 68 per cent and gamma knife are between 26 per cent and 45 per cent.
- Radiosurgery may be effective treatment for selected groups of patients, for example those patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention. This conclusion is consistent with that of other reviews of radiosurgery treatment of AVMs.
- There is insufficient information to determine whether one method of radiosurgery is superior to another as two-year obliteration rates and complication rates appear similar.

The clinical problem

Background

Cerebral arteriovenous malformations (AVMs) are a complex tangle of abnormal cerebral arteries and veins linked by one or more fistulas. AVMs lack a capillary bed and the fistulas allow a high-flow, rapid arteriovenous shunting which can induce arterial hypotension 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). The natural course of AVMs cannot easily be predicted: they may remain static, may grow or may spontaneously regress.

AVMs are often graded to assess likely patient prognosis following treatment. The Spetzler–Martin five-point scale is one of the most common used. It incorporates three variables: the size of the lesion, the type of venous drainage and the location AVM (including proximity to eloquent regions of the brain), as described in Table 4 below.

Table 4 Spetzler–Martin Scale for evaluating prognosis after surgery

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

A crude dichotomisation of risk suggests that patients with a score of 1, 2 or 3 have lower risks of persistent neurological deficits following surgery (< 3%) than those with scores of 4 or 5 (approximately 20%) (Hamilton and Spetzler 1994). Although this scale was originally used to assess microsurgical risk, it has also been used in radiosurgical series to estimate patient prognosis. Some authors have also added a sixth category (VI) – 'inoperable'. There are limitations to a broad application of this score, and it may not be directly applicable to patients treated with radiosurgery.

Epidemiology, clinical presentation and natural history

Cerebral arteriovenous malformations vary considerably in size, location, vascular composition and clinical presentation, such that accurate determination of the likely natural history and prognosis of an individual patient may be very difficult.

The overall prevalence of AVMs in the general population is difficult to ascertain and may be influenced by geographical and racial factors (Valavanis and Yasargil 1998). On the basis of autopsy findings, it has been estimated that the prevalence is between 0.06 per cent (Karhunen et al. 1990) and 0.11 per cent (Jellinger 1986). Incidence has been estimated to be between one and 10 per 100,000 (Crawford et al. 1986a; Ondra et al. 1990). In Australia, this incidence would translate to between 190 and 1,900 new cases per year. It is likely, however, that the number of patients who would present for treatment each year would be fewer than this number, as AVMs may remain asymptomatic for long periods of time.

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.

Haemorrhage is the most common presenting symptom of patients with AVMs, having been reported to occur as the initial manifestation of disease in approximately 50 per cent of patients (Perini et al. 1995). It is possible that the true incidence of haemorrhage is actually higher for these patients, as areas of chronic haemorrhage, which were not clinically detected, may be found during microsurgical procedures (Valavanis and Yasargil 1998).

An annual bleeding rate of 4 per cent for untreated patients has been reported, regardless of the initial clinical presentation (Ondra et al. 1990). Ondra et al., (1990) found, in a prospective evaluation of patients with untreated, symptomatic AVMs, that this haemorrhage rate remained constant throughout a follow-up period of 24 years. 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). A number of other studies have also indicated that the occurrence of a first haemorrhage is associated with an increased risk of subsequent haemorrhage (Pollock et al. 1996). Mast et al., followed a group of 281 unselected, consecutive prospectively enrolled patients who were grouped according to initial clinical presentation: haemorrhage (142) or no haemorrhage (139). They found that the annual rate of bleeding in the haemorrhage group was 18 per cent compared to 2 per cent for the non-haemorrhage group (Brown and Wiebers 1988). Haemorrhage during the follow-up period was significantly associated with haemorrhage as the initial symptom (hazard ratio 7.5, 95 per cent CI 2.2–25.7, p=0.0002) (Mast et al. 1997). Ondra et al., (1990) found an annual mortality rate of 1 per cent and a rate of severe morbidity of 1.7 per cent. Thirty-four per cent (34%) of patients experienced haemorrhage over the 24 years of follow-up, with 85 per cent of those with a bleed either dying or suffering severe morbidity during this time.

Studies correlating angiographic features with clinical presentation of patients with AVMs have demonstrated that there is an increased incidence of haemorrhage for patients in whom the AVM is associated with other structural malformations, such as flow-related aneurysms, stenoses or draining vein occlusions. This can also be said when the AVM is located in deep parts of the brain or in the posterior fossa (Willinsky et al. 1988; Brown et al. 1990; Marks et al. 1990; Albert et al. 1990; Miyasaka et al. 1992; Kader et al. 1994; Turjman et al. 1995; Nataf et al. 1997). Some authors (Graf et al. 1983; Spetzler et al. 1992) have postulated that small and micro-AVMs may be at a higher risk of haemorrhage than larger AVMs due to higher pressure in the feeders and the nidus. Other reports, however, suggest that there is no direct correlation between AVM size and haemorrhage incidence (Crawford et al. 1986a; Willinsky et al. 1988; Ondra et al. 1990; Marks et al. 1990). Small AVMs are more likely to remain asymptomatic before haemorrhage, and more frequently manifest themselves with rupture. In contrast, larger AVMs are more likely to present with seizures or neurological deficits (Valavanis and Yasargil 1998).

Seizures are the second most frequent presenting symptom after haemorrhage. The incidence of seizures is particularly high for those patients with AVMs located on the temporal lobe or those involving the sensorimotor strip (Crawford et al. 1986b). Seizures may also be a clinical manifestation of minor haemorrhage. The risk of haemorrhage in patients with seizures related to their AVMs is lower than in those with previous haemorrhage, but higher than in patients with no history of epilepsy (Graf et al. 1983; Crawford et al. 1986b). Ondra et al. found that patients with AVM-related haemorrhage and patients with seizures had similar long-term morbidity and mortality (Ondra et al. 1990).

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 and Yasargil 1998).

Headache, which is not associated with acute cerebral haemorrhage, is also a relatively frequent symptom experienced by patients with AVMs. Angiographic–clinical correlations have shown that dilated feeding arteries and draining veins which are close to the meninges and the tentorium may be responsible for chronic headaches in these patients. It has also been found that headache incidence is particularly high in those patients with additional dural supply of their AVM and in those with an occipital lesion (Valavanis and Yasargil 1998).

Treatment alternatives for AVMs

It is generally recognised that surgery is an appropriate treatment for some AVMs. Depending on the location of the lesion, it can be approached over the cerebrum, through the skull base or through the ventricular system (AVM Study Group 1999). The primary advantages of microsurgical 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. As discussed, these risks can vary widely from nearly no risk to an unacceptably high risk, where the AVM is deemed inoperable.

Endovascular occlusion (embolisation) was developed to eliminate surgically inaccessible deep or dural feeding arteries. Improvements in technology and expertise with embolisation have meant that lesions previously unsuitable for microsurgical removal may respond to surgery or radiosurgery following embolisation. In some cases AVMs have been eliminated by embolisation alone (AVM Study Group 1999). Catheters can be used to deliver a variety of occlusive agents, including permanent balloons, sclerosing drugs, thrombosing coils and quick acting glues (AVM Study Group 1999). Unfortunately, relatively low rates of complete occlusion or obliteration have been reported with embolisation alone and, as such, embolisation is primarily now used as an adjunctive procedure in combination with radiosurgery or microsurgery. Embolisation has also been used to decrease the size of large lesions prior to surgery or radiosurgery (AVM Study Group 1999).

Stereotactic radiosurgery is another option for AVM treatment, and can involve the use of gamma irradiation (via a gamma knife), proton beam, or linear accelerator (LINAC). As discussed earlier, the procedure involves multiple focused beams directed at the fistula so as to cause vascular injury and subsequent thrombosis, with minimal injury to the surrounding brain tissue. The main advantage of radiosurgery is the avoidance of microsurgery and attendant risks. The primary disadvantage is the long interval (one to three, or more, years) from treatment to therapeutic effectiveness (obliteration), during which time the patient is not protected from haemorrhage. Other disadvantages include variable therapeutic effectiveness for different lesions, the risk of radiation injury and the need for long-term follow-up, including repeat angiography (Barrow 1999)

Existing reviews

A number of technology assessments have addressed the indication of AVMs. The Alberta Heritage Foundation for Medical Research (Schneider and Hailey 1998) reached the following conclusions regarding stereotactic radiosurgery (SRS) for treating AVMs:

> '…generally weak additional evidence to that considered in earlier assessments. SRS is useful in appropriately selected patients, but there appears to be a need for long-term followup, to include consideration of adverse effects…
>
> There is no real indication of the proportion of AVMs that might be appropriately treated by SRS alone or in combination with embolization. In many cases, surgery will remain the preferred option.'

The Agencia de Evaluación de Tecnologías Sanitarias (AETS) (AETS 1997) made similar comments (as applied to all reviewed indications):

> 'Evaluation of the results of radiosurgery are limited by several issues: poor quality of the evidence provided by the studies carried out (mainly description of a number of cases), incomplete description of all the patients treated, heterogeneity of the studies with regard to selection of cases, definition of therapy success or failure and duration of the latency period from the time of treatment to the measurement of the result.'

The authors also drew the following AVM-specific conclusions: that, although thousands of patients had been treated, due to the 1) small clinical differences observed, 2) small number of studies which evaluated clinical effectiveness and 3) the effect of patient selection, it was not possible to establish differences in the effectiveness of linear accelerator and gamma knife radiosurgery techniques.

Literature review

Search Strategy

Radiosurgery publications

The search strategy on page 6 was combined with the following MeSH terms for Medline, PreMedline and HealthSTAR, and was conducted for the period 1990 to March 2000.

- intracranial arteriovenous malformations (exploded) or 'arteriovenous malformations' (exploded) or 'cerebral arteriovenous malformation$' as a key word.

Embase was searched using the equivalent terms of::

- brain arteriovenous malformations (exploded) or 'cerebral arteriovenous malformation$' as a key word.

Microsurgery publications

Microsurgical series which were published during the same period as the radiosurgical series (1990 to March 2000) were identified using a combination of recent review articles and searches of the above databases. The disease-specific terms used for radiosurgery searches were also used and were combined with the terms 'microsurgery (MeSH) or surgery (MeSH) or neurosurgery(MeSH)'. Only nine surgical series were identified where primary clinical results were reported and all have been included here in Table 8.

In addition, articles were retrieved to provide background information about stereotactic radiosurgery and AVM therapy.

Eligibility of studies

A total of 720 abstracts were identified in the literature search, of which 75 were duplicate records retrieved from different databases. The 645 non-duplicate abstracts were evaluated to exclude those definitely not eligible. The criteria below were applied to each abstract. The full article was retrieved for the 140 abstracts which were either potentially eligible or eligible, or for which there was insufficient information available in the abstract to assess eligibility.

Eligibility criteria for studies

- Studies examining the effectiveness of stereotactic radiosurgery treatment of arteriovenous malformations:
  - studies examining radiosurgery treatment of angiographically occult vascular malformations (AOVMs), venous angioma, low/high flow carotid cavernous fistulae and cerebral cavernous malformations were not included.
- English language journal articles reporting primary data obtained in a clinical setting (that is, reviews were not included).
- Study design and methods clearly described:
  - case series of ≥ 10 patients where the authors had attempted to address bias, eg consecutive patients, or where patients could be assumed to be consecutive (that is, all patients within a stated time period); and
  - studies with a more powerful design than case series.
- Published in 1990 or later, to reflect the current status of diagnostic imaging and treatment technologies.
- Or where these inclusion criteria could not be established from the abstract.

The 140 retrieved papers were re-examined using the above criteria, and a further 107 were excluded for the following reasons:

- The paper did not address clinical effectiveness of radiosurgery (eg treatment reviews, modelling).
- No attempt had been made to address selection bias in case series by using consecutive patients, that is, patients appeared to have been selected from a larger patient group or, where this criteria was still unclear, from examination of the full paper.
- Where patients had been selected on the basis of whether they had angiography, papers were included in Table 37 if the authors reported either the total number of patients treated, or the total number of patients eligible for angiography at the specified time point.
- < 10 patients.
- Patients treated did not have AVMs.
- Studies had been superseded by another publication using the same patient group, with the same purpose (see below).

The issue of multiple publications from the same treatment facility became a complex issue in evaluating and assessing available evidence for this indication. A large number of publications, using the same or predominantly the same patient groups have been generated from a small number of treatment centres.

Only studies that were not superseded by a later publication were included in the review. Studies which examined pooled patient groups from several institutions were excluded when the individual institutions had published the same information separately.

Seventeen publications were excluded as they had been superseded by more recent publications of the same patient group. Any earlier publications that provided more comprehensive information than a later publication remain in Table 37 for completeness.

Outcomes

Before conducting the literature review, it was determined that the following outcomes be addressed, if available in the literature. Unfortunately, due to the paucity of good quality clinical data, many of these outcomes could not be evaluated in this review.

Table 5 Outcomes for evaluation in review

Primary outcome measures	
1.	Survival
	• Event free
2.	Obliteration
	• Imaging evidence of obliteration (angiogram)
3.	Intracranial haemorrhage
	• recurrent
4.	Therapeutic index
	• Response rate (successful obliteration): rate of radiation induced complications
Secondary outcome measures	
5.	Procedural success
	• Morbidity/complications
	• Mortality
6.	Quality of life
	• Short-term
	• Longer-term
	Symptoms of disease: eg seizure, headache, neurological deficit
7.	Safety
	• Short-term side effects of treatment
	• Long-term radiation complications

Within the review, the following outcomes are examined: obliteration rates, rates of intracranial haemorrhage, procedural success (morbidity and mortality) and short- and long-term side effects. It is usually agreed that angiography is the most accurate means by which to confirm obliteration of an AVM (Young et al. 1997; Miyawaki et al. 1999; Barrow 1999). As such, in consultation with the supporting committee, it was decided that only angiographically confirmed AVM obliteration, rather than obliteration defined by other imaging, such as MRI or CT, would be accepted as sufficient evidence that the AVM was no longer patent and that haemorrhage risk had been removed.

Results

Is it safe?

Safety outcomes were difficult to evaluate in this review. Papers often did not report information in a consistent manner, and it was often not possible to determine at what time point after treatment the complications developed or were reported, thereby limiting comparison across studies. It is important to note that the methodological limitations of all studies (microsurgical and radiosurgical) and the small sample sizes limit the usefulness and clinical applicability of any information presented here. Patients treated with microsurgery are likely to be different to patients treated with radiosurgery. This is likely to be particularly apparent in earlier radiosurgery case series, where most

patients treated where those ineligible for surgery (Rowed and Nedzelski 1997; Samii and Matthies 1997a)

Table 6 Complications associated with microsurgery treatment of AVMs

Study	N	Procedural Mortality (%)	AVM haemorrhage after surgery (%)	Fatal AVM haemorrhage (%)	New neurological deficit (%)		Other surgical complications (%)
					Permanent	Transient	
(Malik et al. 1996) (Non-temporal lobe AVMs)	132	4	3	–	15	–	2
(Hamilton and Spetzler 1994) (all)	120	–	0	–	8	15	–
Subset of Spetzler Martin Grade I-III only	76	–	0	–	1	2	–
(Hernesniemi and Keranen 1990)	79	1	8	4	9	–	3
(Pikus et al. 1998) (all)	72	0	0	–	8	–	–
Subset of Spetzler Martin Grade I-III only	54	0	–	–	2	–	–
(Sisti et al. 1993) (< 3cm only)	67	0	0	–	2	–	–
(Schaller and Schramm 1997) (< 3cm only)	62	0	2	–	3	27	10
(Pasqualin et al. 1991) (surgery after embol)	49	5	–	–	16	55	16
(Tew et al. 1995) (1 or 2 surgical proc)	39	3	–	–	13	–	–
(Chang et al. 1998) (Surgery after RS)	36	–	–	6	11	17	11
(Malik et al. 1996) (Temporal lobe AVM only)	24	4	4	–	13	–	13

As many papers present results from small case series, extreme percentages should be viewed with caution.

Procedural mortality approached 5 per cent for patients treated with microsurgery in these uncontrolled series. Permanent neurological complications ranged from 1 per cent to 16 per cent of patients, and up to about 50 per cent of patients suffered transient complications (see Table 7). It is difficult to interpret these results due to the small numbers of patients, the uncontrolled nature of the case series and the lack of a consistent definition between papers of what constitutes ‘transient’.

Papers which report results of patient subgroups suggest that patients with Spetzler–Martin Grade I–III AVMs or AVMs where the diameter is < 3cm (that is, groups with better prognosis) have a lower permanent neurological complication rate than the broader surgical population. This should again be interpreted with caution due to the very small patient numbers in this subset.

Complications associated with radiosurgery comprise similar events to microsurgery, however, it is important to examine complications specifically induced by radiation. These can include changes on post treatment imaging, radionecrosis or oedema. Unfortunately many papers provide insufficient information regarding such complications, making any comparison between LINAC and gamma knife difficult. LINAC radiosurgery papers tended to provide more detail regarding safety than did gamma knife papers.

The range of the incidence of new neurological complications was wide for all treatment options. In conducting the review it was noted that LINAC case series tended to report more information on adverse effects and neurological complications, whereas gamma knife case series tended to report predominantly on post-radiosurgery imaging changes, with less information on neurological complications. It was also noted that complication rates for patients receiving neurosurgery may have been dependent upon lesion size. Series reporting results for small AVMs only (< 3cm or Spetzler–Martin grade I–III) had

new permanent neurological complication rates of between about 1 per cent and 3 per cent

Table 7 Complications associated with radiosurgery treatment of AVMs

Study	N	Procedural mortality (%)	AVM haemorrhage after surgery (%)	Fatal AVM haemorrhage (%)	New Neurological deficit (%)		Radiation induced complications (%)			
					Permanent	Transient	Sympto-matic	Imaging changes only	Delayed	Acute
Gamma knife radiosurgery										
(Aoki et al. 1996)	236				4.4		10	20 @ 2yrs		
(Flickinger et al. 1998)	332						9	30		
(Henkes et al. 1998)	64			2						
(Karlsson et al. 1998)	115		3 1.8 pa				Any 12			
(Karlsson et al. 1996)	1604		3 2.1 pa							
(Pendl et al. 1994)	181					< 1		1		
(Pollock et al. 1996b)	315		7 4.8 pa	2						
(Pollock et al. 1998a)	316				Any 6					
(Pollock et al. 1999)	249/ 227		1	< 1	1		< 1			
(Tanaka et al. 1996)	99		2				2			
(Wara et al. 1995)	33									6
(Yamamoto et al. 1995)	121		6	3	5					
LINAC radiosurgery										
(Colombo et al. 1994)	228		7	3			5			
(Duffner et al. 1997)	50		2		2	14		12		
(Engenhart et al. 1994)	212		5	2	3	5	8	9		
(Friedman and Bova 1992)	80		3			3	5			
(Friedman et al. 1995)	158		4	<1	3	5		2		
(Gobin et al. 1996)	125		8	2	2					
(Kirkeby et al. 1996)	25		8				12			
(Loeffler et al. 1990)	16						6	12		
(McKenzie et al. 1993)	112								2	< 1
(Miyawaki et al. 1999)	73		16	7	14				18%	16
(Pelissou-Guyotat et al. 1997)	34				Any 10					
(Pica et al. 1996)	41		5	2	10	17				
(Schlienger et al. 2000)	169		2		< 1	4				
(Sebag-Montefiore et al. 1995)	101		2yr act inc 5.1		5	2				
(Smith et al. 1997)	54		10	2	2					
(Souhami et al. 1990)	33		3				7		9	
(Touboul et al. 1998)	100		10						8	
(Young et al. 1997)	50		4	2	2	2				

As many papers present results from small case series, extreme percentages should be viewed with caution.
Act inc – Actuarial incidence

The range of the incidence of radiation-induced complications for LINAC and gamma knife radiosurgery was also wide. Symptomatic complications ranged between 5 per cent and 12 per cent for LINAC and 2 per cent and 12 per cent for gamma knife. Post radiosurgical imaging changes ranged from 10–19 per cent and 20–30 per cent for

LINAC and gamma knife, respectively. Acute complications affected between 1 per cent and 16 per cent of patients treated with LINAC radiosurgery, and approximately 6 per cent for those treated with gamma knife. Delayed complications for LINAC ranged from approximately 2–18 per cent, with most series reporting around 10 per cent of patients being affected. Delayed complications were not reported in any gamma knife series, it is unclear why.

There is insufficient information from which to draw a definitive conclusion about the safety of radiosurgery compared to microsurgery, or indeed about LINAC radiosurgery versus gamma knife radiosurgery. Methodological limitations, patient selection biases and inconsistencies in adverse event definitions hinder any useful comparison.

Is it effective?

The reviewers were unable to identify any studies where a control group was available; this includes randomised trials, cohort studies or case control studies. The highest level of evidence available was therefore case series (NHMRC Level IV evidence).

In the absence of a randomised controlled trial comparing microsurgical resection to radiosurgery, it is difficult to compare the true efficacy of these two treatment modalities for similar cases. This difficulty is exacerbated by problems with selection bias for both treatment options and a tendency for surgical series to minimise transient post-operative complications (for example, urinary tract infections, pneumonia and infections). The increasing number of radiosurgery centres that are relying on MRI as a replacement for angiography (or as an initial screen prior to angiography) in determining obliteration rates for AVMs also introduces another level of selection bias and complicates assessment further. Rapid changes in surgical techniques can also complicate longitudinal comparison of patient outcomes.

As can be seen from Table 8, microsurgical series indicate a total excision rate of between 85 per cent and 100 per cent. Surgical series which report on smaller AVMs (< 3cm or Spetzler–Martin grade I–III) indicate higher total excision rates and lower complication rates than those series which examine larger or more surgically-inaccessible lesions, or those lesions which have already failed radiosurgical treatment. The obliteration rates of radiosurgical series may be overestimated by only reporting obliterations in those patients who have undergone angiography (as low as 30 per cent of patients). In contrast, post-surgical angiography appears to be routine for almost all patients. The major bias in the microsurgical series is in selecting patients for the procedure. Although ethically appropriate to select those patients for whom surgery is most likely to succeed (and conversely, not to subject patients with unreasonable risk to the procedure), this selection makes it difficult to draw reliable comparisons between microsurgical and radiosurgical treatment.

As can be seen from Table 8, the studies which report on patients with Spetzler–Martin Grade I–III AVMs or AVMs where the diameter is < 3cm (that is groups with better prognosis) suggest that total AVM excision rates are comparable to, or slightly better than the general surgical series.

Table 8 Results of microsurgical resection of arteriovenous malformations

Study	N	Rate of total excision (%)
(Malik et al. 1996) (Non-temporal lobe AVMs)	132	96
(Hamilton and Spetzler 1994) (all)	120	100
Subset of Spetzler–Martin Grade I–III only	76	100
(Hernesniemi and Keranen 1990)	79	89
(Pikus et al. 1998) (all)	72	97
Subset of Spetzler–Martin Grade I–III only	54	100
(Sisti et al. 1993) (< 3cm only)	67	94
(Schaller and Schramm 1997) (< 3cm only)	62	98
(Pasqualin et al. 1991) (surgery after embolism)	49	100
(Tew et al. 1995) (1 or 2 surgical procedures)	39	97
(Chang et al. 1998) (Surgery after radiosurgery)	36	86

The acceptance of radiosurgery as a treatment for AVMs hinges on the belief that it is highly effective at obliterating AVMs within two years of treatment with two-year obliteration rates reported by studies to be at around 80–90 per cent. As the risk of haemorrhage persists until the AVM has been obliterated completely, the longer the interval from treatment to cure, the greater the cumulative risk of intracranial bleed, with its attendant morbidity and mortality. Steiner et al. (Steiner et al. 1992) found by using a Kaplan–Meier estimate of haemorrhage risk after radiosurgery that the rate was approximately 3.7 per cent per annum (up to five years after SRS), almost the same as that for untreated AVMs. This suggests that the risk of haemorrhage after radiosurgery is essentially unchanged for those patients in whom the AVM remains patent.

The low rate of follow-up angiography is a potential issue in considering the results presented in this section. With some studies reporting that follow-up angiography has occurred in as few as 38 per cent of eligible patients (Friedman et al. 1995), the obliteration rates reported, which primarily reflect the number of obliterated AVMs as a percentage of angiograms performed, may grossly overestimate the actual obliteration rate at a given timepoint. Further selection bias may also be introduced by the practice of selecting patients to undergo angiography only if the MRI or CT scan suggests that the AVM has been obliterated. Patients whose MRI or CT scan suggests that the AVM remains patent do not undergo angiography and are subsequently not considered in the data analysis (hence further reducing the denominator of any calculated obliteration rate).

An attempt has been made, in presenting obliteration results in Table 9 and Table 10, to correct for this bias. We have added what we consider important additional information by reporting obliteration rates as a percentage of the number of patients who were eligible for angiographic follow-up at a given time (where reported in the study). As can be seen from the tables, author-reported obliteration rates (at two years post-radiosurgery) ranged from 55 per cent to 81 per cent and 37 per cent to 85 per cent for LINAC and gamma knife radiosurgery respectively. When adjusted to reflect obliteration rates as a percentage of those patients eligible for angiography, LINAC rates drop to between 44 per cent and 68 per cent and gamma knife rates to between 26 per cent and 45 per cent. Few authors attempted to adjust their own estimates to account for these biases:

- Miyawaki et al. reported three-year obliteration rates using three different calculation methods – 1) only angiographic data 2) either angiography or MRI to define both obliteration and failures and 3) only angiographic data for obliterations and angiography, MRI, retreatment (any) or death from haemorrhage as failures. Five-year actuarial rates for each method were also reported (Miyawaki et al. 1999).

- Young et al. reported three-year obliteration rates as a percentage of patients who were eligible for angiography at three years, rather than as a percentage of patients who received angiography at three years (Young et al. 1997).
- Heffez et al. used Kaplan–Meier life-table analysis to estimate obliteration rates (Heffez et al. 1998).

Table 9 LINAC radiosurgery obliteration rates

		12 months				24 months				36 months			
Study	**N**	**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**		**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**		**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**	
		N	%	N	%	N	%	N	%	N	%	N	%
(Colombo et al. 1994)	228	74/156	47	74/170	44	90/113	80	90/142	63				
(Engenhart et al. 1994)	145					53/97	55	53/120	44				
(Friedman and Bova 1992)	80	16/ 41	39	16/48	33	17/21	81	17/25	68				
(Gobin et al. 1996) (RS + embol)	125					41/63	65	41/88	47				
(Kirkeby et al. 1996)	25					14/20	70	14/25	56				
(Loeffler et al. 1990)	10	5/8	63	5/10	50								
(Miyawaki et al. 1999)	73									18/28	64	18/60	30
(Pica et al. 1996)	41	4/29	14	NR	NR	26/32	81	NR	NR				
(Souhami et al. 1990)	33	8/21	38	NR	NR								
(Touboul et al. 1998)	100											3 year actuarial rate 40 ± 5% (n=45)	
(Young et al. 1997)	50											25/50	50

NR – not reported; RS – radiosurgery; embol - embolisation

Table 10 Gamma knife radiosurgery obliteration rates

		12 months				24 months				36 months			
Study	**N**	**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**		**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**		**% Obliteration (% of those with angiography)**		**% Obliteration (% of those eligible for angiography)**	
		N	%	N	%	N	%	N	%	N	%	N	%
(Flickinger et al. 1996a)	316									142/197	72	NR	NR
(Heffez et al. 1998)	82					21/58	37	21/82	26				
(Pollock et al. 1996b)	315					134/210	64	134/295	45				
(Pollock et al. 1998a)	315					134/220	61	134/295	45				
(Pollock et al. 1999)	249 or 227					72/97	74	NR	NR				
(Tanaka et al. 1996)	290	41/79	52	NR	NR	62/73	85	NR	NR				
(Yamamoto et al. 1995)	121	2/51	4	NR	NR	21/51	41	NR	NR	35/51	69	NR	NR

Due to the paucity of good quality published data, it is very difficult to accurately compare treatments. Table 11 attempts to consolidate pertinent information about each treatment method. It is important to note, at this stage, that the post-treatment intracranial haemorrhage rate reported for neurosurgery is a crude percentage, not an annualised rate as reported for the no treatment and radiosurgery options.

Table 11 Comparison of surgical and radiosurgical treatment of AVMs

	Untreated	Neurosurgery		Stereotactic radiosurgery LINAC (at 24months post RS)		Stereotactic radiosurgery Gamma knife (at 24 months post RS)	
	%	% of patients (all patients)	% of patients (small < 3cm or S-M gr I-III only)	% of patients with angiography	% of patients eligible for angiography	% of patients with angiography	% of patients eligible for angiography
Obliteration							
All Patients		85–100	94–100	55–81	44–68	37–85	26–45
No prior therapy		95–100	NR				
After prior therapy		–85	NR	65	47%	NR	NR
Cerebral haemorrhage incidence (post treatment)	2–4 pa	0–7.6	0–2%	1.6–5.1 pa Crude rate: 2–16		1.8 – 4.8 pa Crude rate: 1–7	
Procedural associated mortality		0–5	0%	NR		NR	
Fatal cerebral haemorrhage (crude rate not annualised)	1–2 pa	4–6	NR	< 1–7 (most series report around 2–3%)		1–3	
Morbidity	Approx 3.5						
New neurological complications:							
Any (not specified)				Approx 10 (1 study)		Approx 6 (1 study)	
Permanent		1–16	0.8–3	1–14		1–5	
Transient		2–55	1.7–27	2–17		< 1 (1 study)	
Radiation induced complications:							
Any (not specified)		n/a	n/a	NR		12 (1 study)	
Symptomatic		n/a	n/a	5–12		1–10	
Imaging changes only		n/a	n/a	2–12		1– 30	
Delayed		n/a	n/a	2–18		NR	
Acute		n/a	n/a	< 1–16		6	

NR – not reported

Note: Ranges are based on reported information from the case series, there has been no adjustment or weighting for sample size. As many papers present results from small case series, extreme percentages should be viewed with caution. It should also be noted that the percentage of patients in the neurosurgical series who experience post treatment haemorrhage is a crude percentage, not a per annum rate as with radiosurgery.

The following points can be made:

- It appears that surgery is effective in achieving complete removal of the AVM in upwards of 85 per cent of patients, with an immediate removal of haemorrhage risk at excision, however, this is based on highly selected patients generally with small AVMs.
- Microsurgery excision rates for small (ie < 3cm) or Spetzler–Martin grade I–III AVMs approached 100 per cent, with new permanent neurological complication rates of approximately 1–3 per cent.

- Radiosurgery does not reduce the risk of haemorrhage immediately; the risk does not fall until the AVM is obliterated (often around 2–3 years after radiosurgery). Post treatment intracranial annual haemorrhage rates for LINAC and Gamma knife appear to be similar to those for untreated patients.
- Obliteration rates reported in the literature for both LINAC and gamma knife radiosurgery appear to be an overestimation of the true obliteration rate, due to 1) follow-up of patients is generally incomplete and 2) only a percentage of those patients eligible for angiography at any given time point actually undergo the procedure
- Two-year obliteration rates (as a percentage of patients who undergo angiography) for both LINAC and gamma knife appear to be similar at 55 per cent to 81 per cent and 37 per cent to 85 per cent for LINAC and gamma knife radiosurgery respectively.
- When adjusted to reflect two-year obliteration rates as a percentage of those patients eligible for angiography LINAC rates drop to between 44 per cent and 68 per cent and gamma knife rates to between 26 per cent and 45 per cent.

Conclusions

Due to the generally poor quality of data available, and the variability in the patient populations reported upon, it is not possible to draw definitive conclusions regarding the comparative efficacy of microsurgery versus radiosurgery or LINAC radiosurgery versus gamma knife radiosurgery.

Patients treated with microsurgery achieve complete excision rates of between 85 per cent and 100 per cent, with permanent neurological complication rates of up to 15 per cent.

For the subset of patients with small, easily accessible AVMs (that is, < 3cm or Spetzler–Martin grade I–III), microsurgery appears to be the most appropriate treatment with total excision rates of between 94 per cent and 100 per cent and low permanent neurological complication rates of less than 5 per cent.

Radiosurgical treatment resulted in permanent neurological complications in approximately 2–10 per cent of patients, with little apparent difference in these rates between patients treated with gamma knife and LINAC modalities.

Obliteration rates reported in the literature for both LINAC and gamma knife radiosurgery appear to be an overestimation of the true obliteration rate, due to the fact that

- follow-up of patients is generally less than adequate; and
- only a percentage of those patients eligible for angiography at any given time actually undergo the procedure.

These methodological weaknesses limit our ability to draw reliable conclusions regarding the place of radiosurgery.

Two-year obliteration rates (when reported as a percentage of those patients eligible for angiography) for LINAC are between 44 per cent and 68 per cent and gamma knife are between 26 per cent and 45 per cent.

Radiosurgery may be effective treatment for selected groups of patients, for example those with surgically inaccessible lesions and those with comorbidities which preclude surgical intervention. This conclusion is consistent with that of other reviews of radiosurgery treatment of AVMs.

There is insufficient information to determine whether one method of radiosurgery is superior to another. Two-year obliteration rates for LINAC and gamma knife radiosurgery appear similar, as do complication rates (both permanent and transient).

Cerebral metastases

Summary of findings

- It is difficult to determine the true effect of radiosurgery alone as most patients also received WBRT.
- One randomised controlled trial was identified which compared radiosurgery plus whole brain radiotherapy to whole brain radiotherapy alone in patients with multiple metastases. However, this trial is very small, uses an inadequate randomisation method and is susceptible to several other biases.
- This trial demonstrated improved local control for patients treated with radiosurgery plus WBRT. There was, however, no difference in survival for these patients. Methodological limitations mean this trial is likely to overestimate the efficacy of radiosurgery. The authors report little safety information on these patients.
- The case series added extra useful information as, although not randomised, they often contained considerably more patients than did the randomised trial.
- Complications associated with radiosurgical treatment of cerebral metastases were generally poorly reported in the case series.
- 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.
- Suspected or confirmed radiation necrosis developed as a significant long-term complication in up to 10 per cent of patients. Six per cent required treatment for symptomatic radiation necrosis and in 1 per cent of patients the radiation necrosis was fatal.
- Heterogeneity of case series patient populations and problems with generalisability of the randomised controlled trial precludes definitive conclusions regarding the place of radiosurgery plus whole brain radiotherapy in improving patient survival.
- There is insufficient information to compare the effectiveness of gamma knife radiosurgery and LINAC radiosurgery.
- Survival appears to be similar between patients treated with surgery and whole brain radiotherapy, gamma knife radiosurgery and LINAC radiosurgery, and is likely to be influenced more by baseline prognostic factors than by the type of treatment.

The clinical problem

Many malignant primary tumours are associated with the development of cerebral metastases, either by haematogenous spread from distant lesions or via direct extension from tumours adjacent to the cranial cavity. The most common primary cancers associated with cerebral metastases in adults are, lung, breast, colorectal melanoma and renal cell carcinoma (Anderson and Flynn 1997).

Obtaining accurate incidence and prevalence information for brain metastases is difficult. Recent reviews have suggested that up to 20 per cent of patients with cancer may develop brain metastases (Alexander and Loeffler 1999). The number of patients with brain metastases who receive palliative treatment, however, is likely to be less.

Standard treatments for brain metastases

The outcome for untreated patients is poor, with a mean survival of approximately one month after diagnosis (Posner 1974; Markesbery et al. 1978; Zimm et al. 1981). Most patients with cerebral metastases also have systemic spread of their cancer. Death may be due to progression of cerebral or systemic disease (Cairncross et al. 1980; Borgelt et al. 1980; Zimm et al. 1981; Patchell 1991).

Corticosteroid treatment of brain metastases has been used since the 1960s (Davey 1999) with a clinical improvement in neurological function often seen within 24–48 hours. The use of steroids (primarily dexamethasone) has also been reported to extend median patient survival by approximately four additional weeks over no treatment to approximately eight weeks (Horton et al. 1971; Weissman 1988). Prolonged use of corticosteroids is associated with side effects and patients still generally die from progressive neurological disease. (Horton et al. 1971; Markesbery et al. 1978; Kurtz et al. 1981; Zimm et al. 1981; Patchell 1991; Patchell 1991)

Whole brain radiotherapy has been found to reduce patient symptoms, and prolong survival more effectively than steroids alone. There are a number of published randomised and non-randomised trials of WBRT treatment of single and multiple brain metastases. The results have all essentially been similar: survival is improved by approximately 3–6 months over no treatment (Borgelt et al. 1980; Kurtz et al. 1981; Patchell et al. 1990; Noordijk et al. 1994; Sneed et al. 1996).

Two uncontrolled case series have suggested that retreatment with WBRT may be beneficial for recurrent brain metastases (Kurup et al. 1980; Hazuka and Kinzie 1988). However, only a small number of these patients experience improvement in their neurological symptoms, and further neurological deterioration may result from radiation necrosis (Hazuka and Kinzie 1988).

Two randomised controlled trials of the benefit of surgery in patients with a single brain metastasis have demonstrated significant survival benefits for surgery plus WBRT compared to WBRT alone (Patchell et al. 1990; Noordijk et al. 1994). Median survival for patients treated with surgery and whole brain radiotherapy was approximately 9–10 months compared to 4–6 months for patients treated with WBRT alone. A third randomised controlled trial of surgery plus WBRT versus WBRT alone (Mintz et al. 1996), however, found no survival benefits with the addition of surgery. Median survival for patients treated with surgery plus WBRT was 5.6 months compared with 6.3 months for those patients receiving WBRT alone ($p=0.24$) (Table 12).

A randomised controlled trial of the benefit of WBRT which compared complete surgical resection plus WBRT to complete surgical resection alone in patients with a single brain metastasis indicated that brain recurrence was significantly lower in patients treated with surgery plus WBRT compared to surgery alone (18% vs 70%, $p<0.001$). Patients were less likely to die from neurological causes if they had been treated with surgery plus radiotherapy (14% vs 44%, $p=0.03$), and the median length of time to death due to neurological causes was also longer for these patients (115 weeks compared to 81 weeks, $p=0.03$). Despite this, the overall survival was 48 weeks for surgery plus WBRT and 43 weeks for surgery alone ($p=0.4$)(Table 12).

No randomised trials assessed effect of surgery for removing two or more metastases, or for treating recurrent metastases.

Table 12 Radiotherapy and surgery for a solitary brain metastasis

Treatment (Study)	Design	N	Median survival (months)	Functional independence (months maintained)	CNS death (%)	Mortality[1] and morbidity (%)
WBRT alone						
Patchell 1990	RCT	23	3.5	2	50	4, 17
Noordijk 1994	RCT	31	6	3.5	33	0, 33 (mild to moderate)
Mintz 1996	RCT	43	6.3	NR	28	7, NR
Surgery + WBRT						
Patchell 1990	RCT	25	9.2	8.8	29	4, 8
Noordijk 1994	RCT	33	10	7.6	35	9, 6 (major)
Mintz 1996	RCT	41	5.6	NR	15	10, NR
Patchell 1998	RCT	49	11	8.5	14	NR
Surgery alone						
Patchell 1998	RCT	46	10	8	44	NR

[1] Mortality: % patients who died within 30 days of treatment or who were diagnosed with radiation necrosis.
Functional independence Karnofsky Performance Score (KPS) ≥ 70
RCT – randomised controlled trial
CNS – central nervous system
NR – not reported by authors

Existing reviews

The Veterans' Affairs MDRC Technology Assessment Program (TAP) conducted a comprehensive systematic review of the role of radiosurgery in treating brain metastases (Anderson and Flynn 1997). This review covered 1990 to July 1997, inclusive, and searched the MEDLINE, PreMedline, Health Planning and Administration, HealthSTAR and EMBASE databases. References were reviewed and were included in the systematic review if they met the MDRC TAP inclusion criteria for systematic review which are:

- studies evaluating the effectiveness of stereotactic radiosurgery for brain metastases.
- English language journal articles reporting primary data obtained in a clinical setting, or analyses of primary data maintained in registries or institutional databases.
- study methods and design clearly described.
- case series including ≥ 10 patients, or studies with a more powerful design.
- studies not superseded by a later publication, with the same purpose, by the same group.
- published 1990 or later, to reflect the current status of diagnostic and treatment technologies.

A total of 13 case series met the above inclusion criteria and were considered in the MDRC TAP review. The authors drew the following conclusions:

> 'Lack of data from high quality studies precludes any definitive assessment of the relative effectiveness of SRS [stereotactic radiosurgery] to standard treatment for brain metastases. It also precludes any definitive assessment of optimal equipment selection, treatment parameters or patient selection criteria
>
> The available data from case series reports *suggest* that SRS is a relatively safe and effective technology for the definitive treatment of brain metastases in selected patients. It appeared to offer considerably greater survival benefits than traditional whole brain radiotherapy. SRS may be comparable to surgery plus radiation therapy for the treatment of patients with smaller solitary metastases. SRS can be used to treat patients whose metastases recur after traditional therapies, a group for whom definitive treatment options are frequently unavailable. As with other definitive therapies for patients with brain

metastases, highly functional patients with well controlled systemic cancers derive the greatest benefit from treatment.

…valid comparisons of the relative effectiveness of treatment options are not possible using existing research…

…In the absence of data from high quality studies, uncertainty remains about the true effectiveness of SRS for the treatment of metastases to the brain. One randomized clinical trial is in progress, and further trials are needed, to address the many unanswered questions about the use of SRS for this application. Such trials will provide stronger evidence on which to base clinical and policy decisions.'

Literature review

Search Strategy

The search strategy on page 6 was combined with the following MeSH terms for Medline, PreMedline and HealthSTAR, and was conducted for 1990 to March 2000.

'Brain neoplasms' (exploded) or ('brain metastases' or 'intracranial metastases' or 'metastatic brain tumors' or 'cerebral metastases') as key words.

Embase was searched using the equivalent terms of 'brain metastasis' (exploded) or 'brain metastasis' as a key word.

In addition, articles were also retrieved to provide background information about stereotactic radiosurgery and brain tumour therapy.

Eligibility of studies

As the MDRC TAP systematic review (Anderson and Flynn 1997) was considered to be methodologically sound, a decision was made to update this review rather than to repeat it. For this reason, we restricted our review to publications published from 1997 to March 2000, when our search was conducted. Titles and abstracts of 131 references were screened. Forty-five references were determined to be relevant, and their full text articles were reviewed for potential inclusion in the systematic review. The same inclusion criteria as those used by MDRC TAP (above) were used to assess the retrieved papers, with the additional criterion of only including case series where the authors had attempted to address selection bias by including consecutive patients.

One randomised controlled trial of stereotactic radiosurgery plus whole brain radiotherapy (WBRT) versus whole brain radiotherapy alone for treating multiple brain metastases was identified (Kondziolka et al. 1999). Methodological characteristics of this trial are tabulated below. There were no published randomised controlled trials of radiosurgery (RS) ± WBRT in treating single brain metastasis, however, one ongoing randomised trial in this indication was identified. No direct comparisons of the LINAC versus the gamma knife methods of radiosurgery were identified. Seventeen case series met the inclusion criteria for the review and are tabulated in Table 39.

Table 13 Methodological characteristics of randomised controlled trial

Authors	(Kondziolka et al. 1999)
Design	RCT single institution
N	27
Randomisation method	Coin toss at initial visit (*inadequate method, open to selection bias*)
Timeframe of patient recruitment	Not reported
Treatment arms	Radiosurgery + WBRT (n=13) WBRT alone (n=14)
Assessment of outcomes	Scans: blinded independent observer Data: investigator independent from each treatment arm (*unclear whether blinded*)
Inclusion criteria	histological confirmation of tumour type, all brain metastases ≤ 25mm mean diameter and > 5mm from optic chiasm 2, 3 or 4 lesions only Karnofsky performance status of ≥ 70
Outcomes	Primary Imaging defined control of brain disease Secondary Overall survival Progression free survival Treatment morbidity Need for additional brain treatments

Outcomes

Before conducting the literature review, we determined that the following outcomes be addressed, if available in the literature. Survival and lesion control were reported fairly consistently, however, limited information was available to assess quality of life of patients treated with radiosurgery.

Table 14 Outcomes for evaluation in review

1. Survival
2. Control of lesion/ freedom from progression
3. Quality of life
• Short-term
• Longer-term
4. Symptoms of disease
• Side effects of treatment

Results

Is it safe?

Controlled evidence

The authors of the randomised controlled trial report that no neurologic or systemic morbidity related to stereotactic radiosurgery was observed (Kondziolka et al. 1999). Patients treated with whole brain irradiation developed hair loss and mild scalp erythema. Given the small number of patients, these results are not unexpected.

Uncontrolled evidence

One paper comparing two retrospective series of patients treated with surgery plus WBRT to those treated with radiosurgery (Muacevic et al. 1999) reported procedural mortality rates, with 1.9 per cent (10 of 52) mortality for surgery plus WBRT and 1.8 per cent (10 of 56) mortality for radiosurgery. These rates are not directly comparable

because of likely differences between the patients treated by each procedure. Patients treated surgically are more likely to have smaller, more superficial lesions with a better prognosis. It is also likely that some patients who underwent radiosurgery were ineligible for surgery because of comorbidity or other reasons. A second paper (Sneed et al. 1999) reported that 1 per cent (1 in 105) of patients treated with radiosurgery developed fatal radionecrosis. Fernandez-Vicioso and colleagues (Fernandez-Vicioso et al. 1997) also reported that 2 per cent of patients developed fatal intratumoural haemorrhage.

Many of the case series in Table 39 provide little detail regarding the type of complications patients treated with radiosurgery experienced. Rather, they provide an indication of whether any adverse effects were acute (often resolving within 72 hours of radiosurgery), transient/sub-acute (2–6 months) or chronic/permanent. It is important to bear in mind however, that the authors' definitions of 'transient' vary between studies.

Treatment-related events from the radiosurgery case series are tabulated in Table 15.

Table 15 Treatment related adverse effects (from radiosurgery case series)

Event	% patients	Reference [number of patients]
Acute complications		
Radiation induced oedema/swelling	18	(Cho et al. 1998) [n=73]
Nausea, vomiting dizziness	5–7	(Schoeggl et al. 1999) [n=45] (Lavine et al. 1999)
Increased or new seizures	6–9	(Grob et al. 1998) [n=45] (Lavine et al. 1999)
Increased paresis	7	(Lavine et al. 1999) [n=45]
Unspecified	9	(Muacevic et al. 1999) [n=56]
Transient or self limiting complications		
Radiation induced oedema	5–18	(Schoeggl et al. 1999) [n=236] (Kim et al. 1997; Pirzkall et al. 1998; Schoggl et al. 1998)
Radiogenic complications	7	(Muacevic et al. 1999) [n=56]
Unspecified	6–15	(Sneed et al. 1999) [n=48] (Fernandez-Vicioso et al. 1997)
Significant or long term complications		
Fatal radiation necrosis	1	(Sneed et al. 1999) [n=105]
Radiation necrosis requiring treatment	6	(Sneed et al. 1999) [n=105]
Suspected or confirmed radiation necrosis (unclear whether treated)	Approx. 1–9	(Pirzkall et al. 1998) [n=35] (Cho et al. 1998; Schoggl et al. 1998; Mori et al. 1998a; Grob et al. 1998)
Intratumoural haemorrhage	3	(Kim et al. 1997) [n=78]
Fatal Intratumoural haemorrhage	2	(Fernandez-Vicioso et al. 1997) [n=48]
Unspecified	4–8	(Tokuuye et al. 1998) [n=48] (Fernandez-Vicioso et al. 1997) [n=48]

Significant or long-term complications from radiation necrosis occur in about 10 per cent of patients. This may be an underestimation of the true number of long-term radiation-induced complications in these patients, as it is likely that patients will die from systemic or cerebral disease before long-term complications develop.

Is it effective?

Controlled evidence

One published randomised controlled trial comparing whole brain radiotherapy plus stereotactic radiosurgery to radiotherapy alone in the treatment of patients with multiple brain metastases was identified.

Randomisation method

The randomisation method for this trial consisted of a coin toss at the patient's first visit. It is unclear whether the treating physician/study staff or someone external to the study performed this coin toss. This method of randomisation is considered unreliable if the coin is tossed by the person determining the eligibility of the patient.

Inclusion criteria

Inclusion criteria are clearly reported.

Sample size, power calculations and statistical methodology

Sample size and power calculations are clearly stated in the report, and the statistical methodology is well described. Sample size calculations were based on a power of 0.80 to detect a difference in the primary outcome measure of local control after RS + WBRT (expected control of 90 per cent) versus WBRT (expected control of 50 per cent). A sample size of 44 patients was estimated. A single interim analysis was scheduled at the 60 per cent accrual point, with a facility to stop the trial if the differences were significant. The level of significance required for stopping the trial is not reported.

Outcome assessment

The primary outcome measure for this trial was imaging-defined control of brain disease, assessed by change in size and number of tumours at 1.5, 3, 6, 9, 12, 15 and 18 months after completion of radiotherapy or radiosurgery. The authors report that this primary outcome was chosen rather than survival, since survival was believed to be related to extrinsic factors (other organ involvement) independent of brain treatments. As previous studies have reported that approximately ¼ to ½ of patients with brain metastases will die as a result of neurological causes (Cairncross et al. 1980; Patchell et al. 1990; Mori et al. 1998a; Muacevic et al. 1999), cause-specific mortality (that is, CNS death) is a reasonable outcome. However, overall survival and quality of life are the most important outcomes.

Imaging was performed as serial magnetic resonance images and the serial scans were read by an independent blinded observer. Secondary outcomes included overall survival, progression free survival, treatment morbidity and need for additional brain therapy. The authors report that data were collated and reviewed by an investigator independent from each treatment arm. It is not stated whether this investigator was blinded to the patients' treatment schedule.

Patient characteristics

Twenty-seven patients were randomised before accrual was stopped after the interim analysis. Baseline characteristics of patients are displayed in Table 17. Patients appeared to be well matched with respect to age, sex and Karnofsky Performance Score (KPS). Overall, 71 per cent of the WBRT alone group had active systemic disease, compared to 62 per cent of the WBRT + RS group. In addition, 21 per cent of the WBRT alone group had more that two metastases, compared to 38 per cent of the WBRT + RS group.

Table 16 Clinical characteristics of patients with multiple brain metastases

	WBRT alone	WBRT + RS
Mean age (range)	58 (33–77)	59 (46–74)
Male:Female	7:7	9:4
Median KPS	100	100
Tumour histology		
Lung carcinoma	7	5
Melanoma	3	2
Renal cell carcinoma	2	2
Breast carcinoma	2	2
Other	–	2
Systemic disease		
None (other than brain)	4	5
Any	10 (71%)	8 (62%)
Present (but not lung)	5	4
Present (including lung)	5	4
Number of tumours		
Two	11 (79%)	8 (62%)
Three	1	3
Four	2	2

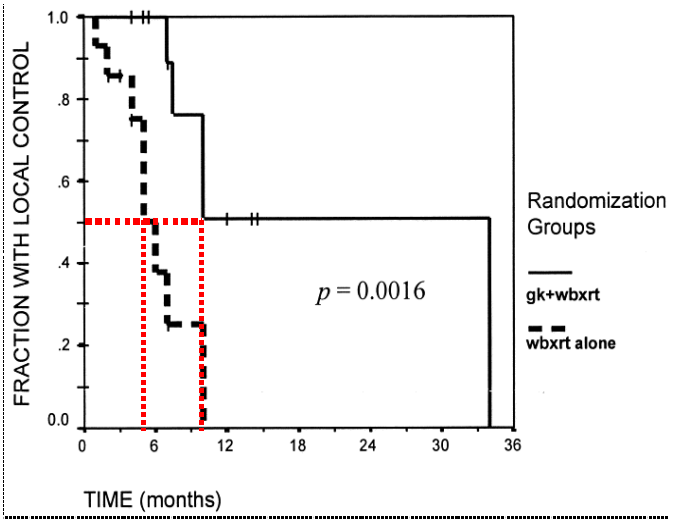
WBRT – whole brain radiotherapy
RS – radiosurgery
KPS – Karnofsky Performance Score

Results

Local tumour control

The trial was stopped following an interim analysis at 27 patients (60% accrual). A log-rank analysis at this point indicated a significant benefit in the rate of local control after radiosurgery plus WBRT (p=0.0016) (Figure 2)

Figure 2 Kaplan–Meier plot of local tumour control over time (radiosurgery [GK] plus WBRT versus WBRT alone)



Source: (Kondziolka et al. 1999)
WBRT or WBXRT – whole brain radiotherapy
GK – gamma knife radiosurgery

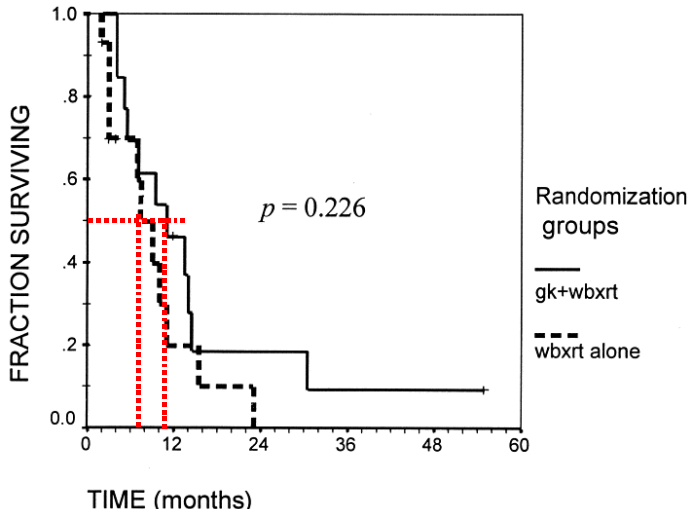
The median time to local failure was six months after WBRT alone compared to 36 months WBRT + RS. Any definitive conclusions drawn by the authors are likely to be

unreliable given the very small number of events and the shape of the curves in Figure 1 and 2.

Overall survival

There was no difference in survival although the authors reported that there was a trend favouring WBRT +RS. As can be seen from the dotted lines on Figure 3, and the shape of the survival curves, there is no difference between treatment arms.

Figure 3 Kaplan–Meier plot of patient survival based on initial brain tumour management (radiosurgery [GK] plus WBRT versus WBRT alone)



Source: (Kondziolka et al. 1999)
WBRT or WBXRT – whole brain radiotherapy
GK – gamma knife radiosurgery

The effect of a number of clinical characteristics including tumour histology, number of metastases and type and extent of systemic disease on patient survival was evaluated for the whole group of patients (that is, separate comparisons were not performed for patients in the two treatment groups).

No adjusted analyses accounting for differences in prognostic factors (for example, tumour histology, number of metastases and presence of systemic disease) are reported. It is not possible to determine whether any of these factors may have altered response to treatment. Differences in these factors are likely to be more important in determining response to treatment than are differences in the actual treatment.

Other outcome measures

Although the need for additional brain treatments was indicated as a secondary outcome measure, the authors do not provide details of this outcome. The authors also provide no indication of progression free survival (another designated secondary outcome measure).

Assessment

Despite this trial being the only published randomised trial comparing WBRT and WBRT + RS, there are a number of issues that should be borne in mind when considering the results.

The randomisation method used (a coin toss) is less than ideal, with the potential to be influenced by the person tossing the coin. Any influence may have resulted in selection bias (as discussed previously), and therefore systematic differences between study groups. If randomisation is inadequate we cannot be sure that any observed differences are truly due to differences in the treatment and not due to the selection of particular patients to receive a given therapy (Hennekens and Buring 1987).

The planned sample size of this trial was very small (44 patients), and recruitment was stopped after only 27 patients had been randomised.

The authors do not provide an indication of the proportion of patients who were lost to follow-up or who were available for evaluation at each time point.

The small number of patients and other methodological weaknesses that are likely to overestimate the benefit of radiosurgery make this trial highly susceptible to bias, and severely limit the utility of the results.

Ongoing randomised controlled trials

One ongoing phase III randomised controlled trial of WBRT with stereotactic radiosurgery boost versus WBRT alone in patients with one unresected (or subtotally resected) brain metastasis was identified using the National Cancer Institute CancerNet Physician Data Query (PDQ) database: the RTOG-9508 trial (Radiation Therapy Oncology Group 1999). Patients are stratified according to centre and presence or absence of extracranial disease, and are randomised to one of two arms. Patients randomised to Arm I receive fractionated external beam whole brain irradiation (WBRT) five days each week for three weeks. Patients who still have a solitary lesion with a diameter ≤ 4cm also receive stereotactic radiosurgery within seven days of completing WBRT. Patients randomised to Arm II receive WBRT alone. Patients are followed every three months for one year, then every four months for two years, and then annually. A total of 262 patients will be accrued over 2.5–3.75 years, with interim analyses after 33 per cent and 67 per cent of patients have been followed for six months.

Uncontrolled evidence

Seventeen additional case series were identified for the period 1997 to March 2000. The results of these series are summarised in Table 39. Patient characteristics, incompletely described in most studies, are likely to play a large part in determining the results of treatment.

Most patients included had good performance status, although incomplete reporting made it difficult to determine baseline status in some patients. Three series (Pirzkall et al. 1998; Mori et al. 1998a; Weltman et al. 2000) included patients whose functional status (as measured by the KPS) was ≥ 50, compared to most other studies where patients had a KPS of ≥ 70.

The extent of systemic disease also varied between studies. Muacevic (1999) and Williams (1998) included only patients with controlled or absent primary and systemic disease. Other studies varied quite considerably in the proportion of patients with active systemic disease at baseline from approximately 30 per cent of patients to 75 per cent of patients.

Most papers report on a mix of primary tumour types. Five papers (Gieger et al. 1997; Mori et al. 1998b; Seung et al. 1998; Grob et al. 1998; Lavine et al. 1999) included only patients with brain metastases associated with metastatic melanoma; Schoggl (1998) and

Mori (1998a) reported only on patients with metastases associated with renal cell carcinoma and Kim and colleagues (1997) included only non small-cell lung cancer patients. Muacevic (1999) and Fernandez-Vicioso (1997) reported on patients with single metastatic lesions only, while all other authors reported case series containing patients with either single or multiple (up to five) metastases.

Reported outcomes from case series

Local Control

Most case series reported crude local control rates (generally measured at 30 days post-treatment) of between 80 per cent and 100 per cent of tumours and approximately 80 per cent and 90 per cent of patients (five series only). Gieger (Gieger et al. 1997) reported local control rates of
57 per cent for melanoma metastases and Williams (Williams et al. 1998) reported 52 per cent for non-lung cancer metastases, although both these series had very small patient numbers (12 and 16 patients with 21 and 27 metastases respectively).

Two series reported a median time to local progression: Schoeggl (Schoeggl et al. 1999) seven months (n=23) and Kim (Kim et al. 1997) 30 months (n=78). Reported local control rates at one year ranged from 73 per cent to 89 per cent over all series.

Survival

The median survival following radiosurgery is approximately six to 12 months. The two series that included patients with solitary metastases only reported similar median survival to those that included patients with multiple metastases. Actuarial survival at one year ranged from 19 per cent to 48 per cent.

Table 17 summaries the patient outcomes from the case series reports in Table 39.

Table 17 Summary of outcomes data from case series reports

	Solitary metastases		Solitary or multiple metastases														
Study no. (Table 40)	2	17	1	3	4	5	6	7	8	9	10	11	12	13	14	15	16
N	56	48	65	97	105	45	236	23	35	73	35	60	64	30	55	78	12
Median survival (months)	8	8	7	6	–	8	6	11	11	8	7	7	8	8 8[1]	9	10	8
% one year actuarial survival	43	37	–	26	46 48[2]	–	30 19[2]	48	43	32	–	21	33	–	34	36	37
% local control or weeks to failure of control	95	81	–	91	84 79[2]	97	–	96	90	–	98	90	–	100 52[1]	–	85	57
% one year actuarial control	83	73	–	–	79 71[2]	–	92 89[2]	–	–	80	–	–	91	–	76	–	–

1 authors split results into lung/non-lung metastases, respectively
2 authors split results into radiosurgery + WBRT and radiosurgery alone, respectively

Factors associated with improved treatment outcomes

Twelve case series performed statistical analyses to determine possible patient and treatment factors that were associated with improved patient survival. Although it is not possible to draw any definitive conclusions, a number of variables appeared consistently.

These included patient's neurological performance status (a higher KPS was associated with improved survival), status of systemic or extracranial disease (none or stable disease was associated with improved survival), age (younger patients had improved survival) and lesion size (smaller lesions were better). A number of other indicators were reported in single studies. No associations were found between increased length of survival and the factors of gender, radiation dose, site of the metastases, metastatic histology, time to metastasis, initial (vs recurrent) tumour status, or prior craniotomy. Results from these analyses are presented in Table 18.

Only two papers examined the association with improved local control. Fernandez-Vicioso et al. (1997) found that local control was positively associated with newly diagnosed (versus recurrent) lesions and Sneed et al. (1999) found that brain Freedom from Progression (FFP) (including local failures and new brain lesions) was associated with number of lesions treated and interval from primary diagnosis to brain metastasis diagnosis. No other studies examined predictive factors of improved local control. It is interesting to note that, of these factors, only number of lesions was associated with improved survival in one of the case series.

It is important to realise that in uncontrolled case series, differences in these factors are more likely to account for differences in treatment response than the actual treatment itself.

Table 18 Potential predictive factors from case series associated with improved survival (multivariate analyses only)

	Patient characteristics			Disease characteristics							Treatment characteristics						
No. of study	age	sex	functional status (KPS)	systemic disease status	lesion diameter/volume	number of metastases	site of metastases	metastasis histology	initial vs recurrent	primary site	time to metastasis	total target volume	maximum/total dose	treatment plan (± WBRT)	chemo/immuno-therapy after RS	prior craniotomy	Resection of primary site prior to RS
1 Weltman 2000	✓		ns	✓	✓	ns	ns							✓			
2 Muacevic 1999	ns		✓	ns				ns			ns						
3 Schoeggl 1999	ns	ns	✓	✓		ns					ns						
4 Sneed 1999	ns		✓	✓		ns						✓					
6 Pirzkall 1998	✓		✓	✓	✓	ns								ns			
8 Mori 1998a	✓		ns	✓	ns										✓		ns
9 Cho 1998	ns		ns		ns	ns						ns	ns				
11 Mori 1998b	ns	ns	ns	✓	ns	✓	ns		ns					ns	ns	ns	
12 Tokuuye 1998	ns	ns	✓	✓		ns	ns	ns	ns	✓		ns	ns				
14 Seung 1998			ns	ns								✓					
15 Kim 1997	ns	ns	ns	✓	✓	ns	ns	ns							ns	ns	✓
17 Fernandez-Vicioso 1997	✓		✓														

✓ – a significant predictor
ns – variable tested but not significant
KPS – Karnofsky Performance Score
WBRT – whole brain radiotherapy
RS – radiosurgery

Discussion

Effectiveness of stereotactic radiosurgery for brain metastases

The methodological weaknesses and small sample size of the only randomised controlled trial and the heterogeneity of the case series data preclude a definitive assessment of the effectiveness of radiosurgery in treating brain metastases. Generalisability of the findings is limited.

The small randomised controlled trial demonstrated improvements in local tumour control with radiosurgery plus WBRT compared to WBRT alone. These improvements, however, did not translate into significant survival benefits for patients. This trial is likely to overestimate the benefits of stereotactic radiosurgery.

Some local control of tumour growth was achieved for most patients in the uncontrolled case series, although the duration of this control was quite variable.

The median length of survival from radiosurgery treatment ranged from six to 11 months, which is comparable to the randomised trials of surgery plus WBRT.

There did not appear to be any difference in outcomes of patients treated for a solitary metastasis or multiple metastases. Having said this though, any difference would have been difficult to elucidate as many of the case series reports on patients with single and multiple metastases in the same data set without separating results. The ongoing randomised trial of patients with a solitary metastasis may be important in determining whether patients with a single lesion respond differently to treatment than patients with multiple lesions.

The potential benefit derived by treatment did not appear to differ greatly between patients with recurrent metastases or patients undergoing initial treatment. Again, however, this is difficult to quantify as many trials included both initial and recurrent patients.

There also did not appear to be a great deal of difference in outcomes between patients treated with radiosurgery alone compared to those treated with a combination of radiosurgery and WBRT. It is not possible to draw any definitive conclusions, however, as only a very small proportion of patients received radiosurgery alone, with most series reporting results from all patients together.

A review of prognostic factors associated with improved survival suggested that patients with good baseline performance status (KPS usually) and absent or controlled extracranial disease may live longer than patients without these factors. These findings are consistent with those reported for radiotherapy (Gaspar et al. 1997) and surgically treated patients (Patchell et al. 1990; Noordijk et al. 1994). All patients in the surgical trials and many of the radiosurgery patients had reasonably good baseline performance status.

Based on this case series data it is not possible to draw any conclusions about the relative effectiveness of LINAC and gamma knife radiosurgery in the treatment of brain metastases.

Effectiveness of stereotactic radiosurgery versus conventional treatments

The paucity of the data available also limits our ability to assess radiosurgery relative to other treatment options.

There is more information about different treatment options for patients with a solitary metastasis than for patients with multiple lesions. For this reason, Table 19 below, presents outcomes from four treatment options for patients with a solitary metastasis. This data suggests that outcomes of radiosurgery were similar to those of surgery plus WBRT, with similar attendant morbidity and mortality. Both radiosurgery and surgery had improved outcomes compared to whole brain radiotherapy alone. This comparison must, of course, be interpreted with caution as differences in patient selection are likely to be as important as differences in treatment.

There is a considerable shortfall of information that would facilitate a comparison of radiosurgery to other therapeutic options for multiple metastases. There are no randomised trials of surgery (with or without radiotherapy) for this group of patients. The results of the one randomised trial comparing radiosurgery plus whole brain radiotherapy to whole brain radiotherapy alone have been reported elsewhere in this review. As previously discussed, the methodological shortfalls and highly specific patient population limit the applicability of the results of this trial to patients seen in clinical practice.

Table 19 Radiotherapy, surgery and radiosurgery for solitary brain metastases

Treatment (Study)	Design	N	Median survival (months)	Functional independence (months maintained)	CNS death (%)	Mortality [4] and morbidity (%)
WBRT alone						
Patchell 1990	RCT	23	3.5	2	50	4, 17
Noordijk 1994	RCT	31	6	3.5	33	0, 33 (mild to moderate)
Mintz 1996	RCT	43	6.3	NR	28	7, NR
Surgery + WBRT						
Patchell 1990	RCT	25	9.2	8.8	29	4, 8
Noordijk 1994	RCT	33	10	7.6	35	9, 6 (major)
Mintz 1996	RCT	41	5.6	NR	15	10, NR
Patchell 1998	RCT	49	11	8.5	14	NR
Muacevic 1999[1]	Combined case series	52	16	NR	37,[2] 35[3]	2, 8 (perioperative complications)
Surgery alone						
Patchell 1998	RCT	46	10	8	44	NR
Radiosurgery alone						
Muacevic 1999	Combined case series	56	8	NR	39,[2] 29[3]	2, 9 (perioperative complications)
Radiosurgery ± WBRT						
Fernandez-Vicioso 1997	Case series	48	8	NR	NR	8, 8 (long-term)

[1] Surgery + WBRT patients who would have been eligible for radiosurgery (< 3.5cm lesion diameter; stable systemic disease)
[2] Actuarial neurological death rate after one year
[3] Crude neurological death rate
[4] Mortality: % patients who died within 30 days of treatment or who were diagnosed with radiation necrosis
Functional independence – KPS ≥ 70
NR – not reported by authors
RCT – randomised controlled trial
CNS – central nervous system

Conclusions

Most of the papers that have been included to assess the effectiveness of radiosurgery also include patients treated with whole brain radiotherapy. For this reason, it is difficult to determine the true effect of radiosurgery alone.

One randomised controlled trial was identified which compared radiosurgery plus whole brain radiotherapy to whole brain radiotherapy alone in patients with multiple metastases. However, this trial is very small, uses an inadequate randomisation method and is susceptible to several other biases.

The results from this trial indicated that patients treated with radiosurgery plus whole brain radiotherapy experienced improved local control compared to patients treated with whole brain radiotherapy alone. This improvement in local control however, did not translate into significant survival benefits for these patients. Methodological limitations mean this trial is likely to overestimate the efficacy of radiosurgery. The authors report little safety information on these patients.

The case series added extra useful information as, although not randomised, they often contained considerably more patients than the randomised trial.

Complications associated with radiosurgical treatment of cerebral metastases were generally poorly reported in the case series.

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.

Suspected or confirmed radiation necrosis developed as a significant long-term complication in up to 10 per cent of patients. Six per cent required treatment for symptomatic radiation necrosis and in 1 per cent of patients the radiation necrosis was fatal.

A number of case series analysed treatment and patient factors which were associated with improved patient survival. A higher KPS and controlled or absent systemic or extracranial disease were associated with improved patient survival. Differences in these factors make assessment of the true effect of treatment in uncontrolled studies very unreliable.

Heterogeneity of case series patient populations and problems with the generalisability of the randomised controlled trial precludes definitive conclusions regarding the place of radiosurgery plus whole brain radiotherapy in improving patient survival.

There is insufficient information to compare the safety and effectiveness of gamma knife radiosurgery and LINAC radiosurgery.

Survival appears to be similar between patients treated with surgery and whole brain radiotherapy, gamma knife radiosurgery and LINAC radiosurgery, and is likely to be influenced more by baseline prognostic factors than by the type of treatment.

Acoustic neuroma

Summary of findings

- Microsurgical resection appears to offer similar outcomes to radiosurgery treatment, particularly for patients with relatively small tumours. Microsurgery remains an acceptable therapeutic intervention for most patients with complete resection rates of close to 100 per cent (in patients selected for surgery), facial nerve complication rates of up to 20 per cent at one year, and useful hearing preservation rates of between 30 per cent and 90 per cent. Overall performance is highly dependent on the skill and expertise of the surgeons.
- Radiosurgical intervention produces similar results with tumour control rates of close to 100 per cent and with facial nerve complication rates and useful hearing preservation rates similar to those reported for microsurgery.
- It is likely that the outcomes will depend more on the treatment team expertise, quality of imaging and treatment planning than on the method used to deliver the radiation or the surgical approach.
- Radiosurgery may be effective treatment for selected groups of patients, for example those patients with surgically inaccessible lesions and those with comorbidities which preclude surgical intervention.
- There appears to be little difference in outcome between gamma knife and LINAC radiosurgery, although small patient numbers and methodological limitations preclude any definitive conclusions.

The clinical problem

Acoustic neuromas (vestibular schwannoma, acoustic neurinoma, nerve sheath tumour) arise from the Schwann cells lining the vestibular branch of the eighth cranial nerve (cochlear nerve). They are histologically benign and are characterised by slow growth. They may, in some cases, be locally destructive by eroding the internal auditory canal and by compressing cranial nerves (Varlotto et al. 1996).

Epidemiology

Acoustic neuromas account for approximately 6–10 per cent of primary intracranial tumours (Schuknecht 1974; UCSF Acoustic Neuroma Team 1998), and arise with an incidence of approximately one per 100,000 per year (Nestor et al. 1988; Consensus Development Panel 1994). This incidence translates to approximately 190 new cases in Australia each year, although the number of patients who require treatment may be lower than this. Acoustic neuromas are reported to 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 et al. 1998). They have been reported in all age groups, however, they appear to be more common in people aged 40–59 years.

Acoustic neuromas occur in two forms: sporadic and those associated with neurofibromatosis-2 (NF-2). Sporadic tumours are unilateral and account for approximately 95 per cent of patients, while NF-2 associated lesions are typically bilateral and account for approximately 5 per cent of patients (UCSF Acoustic Neuroma Team

1998). Age of diagnosis appears to differ between the two tumour types. Sporadic acoustic neuroma tends to occur mainly around 45–50 years (UCSF Acoustic Neuroma Team 1998), whereas NF-2 associated tumours tend to occur in younger patients, around 30 years of age (Glasscock et al. 1992).

NF-2 is a rare disease, with a prevalence of approximately one per 100,000 people. NF-1, on the other hand, is more common, with a prevalence of 30–40 per 100,000 people. Virtually all patients with NF-2 will develop bilateral acoustic neuromas, these tumours are rare in patients with NF-1.

It has been suggested that acoustic neuroma associated with NF-2 may have a different natural history from spontaneous (not associated with NF-2) acoustic neuromas. Although we do not present results specifically for NF-2 patients, it should be noted that these patients may also respond differently to treatment. Many publications include both NF-2 and non-NF-2 patients, and results are generally not split accordingly. It should be kept in mind that the distribution of NF-2 patients may influence the overall results reported for each series, for example, it is possible that patients who demonstrate tumour progression may be predominantly NF-2 patients.

Clinical presentation and course

The symptoms associated with intracanalicular tumours are typically limited to the VIIIth cranial nerve: hearing loss, tinnitus and vestibular dysfunction including vertigo. As a tumour progresses, hearing loss worsens and the vertigo is gradually replaced with dysequilibrium. Trigeminal symptoms commence at approximately the same time as brain stem compression, and symptoms are usually limited to mid-facial hypoaesthesias. Ataxia may also begin at this time. As the brain stem compression becomes severe, hydrocephalus may occur, resulting in visual loss and persistent headache.

Table 20 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)

Hearing loss and tinnitus

Hearing loss occurs in well over 95 per cent of patients and is by far the most common presenting symptom of acoustic neuroma. In most cases the mechanism is via compression or direct infiltration of the auditory nerve fibres. In most patients hearing loss is progressive and gradual over many years, often leading to deafness in the tumour affected ear. Up to 10 per cent of patients report a sudden loss of hearing (NIH Consensus Development Panel 1991). It is typically unilateral (except in the case of NF-2 patients), and in early stages involves the preferential loss of high frequencies, with

concordant proportional loss of speech discrimination (UCSF Acoustic Neuroma Team 1998). Tinnitus is frequently reported in patients with acoustic neuroma, and is generally high pitched and confined to the tumour ear. It is generally associated with hearing loss and only a few patients present with unilateral tinnitus in the absence of hearing loss.

Vertigo and dysequilibrium

True vertigo is not commonly associated with acoustic neuroma, with as few as one in five patients reporting this symptom (Selesnick et al. 1993). Most of the patients reporting this symptom have small tumours, with notably fewer patients with large tumours at diagnosis exhibiting this symptom.

Dysequilibrium is much more prevalent than vertigo, occurring in nearly half acoustic neuroma patients (Selesnick et al. 1993). Where the incidence of vertigo decreases with increasing tumour size, dysequilibrium becomes more frequent. Patients with larger tumours (> 3cm diameter) have over 70 per cent incidence of this symptom (UCSF Acoustic Neuroma Team 1998).

Facial aesthesias, pain, and weakness

Dysfunction of the facial sensation occurs in approximately half of tumours over 2 cm in size, and almost never in patients with smaller lesions (Selesnick et al. 1993; UCSF Acoustic Neuroma Team 1998). Hypoaesthesia of the mid-facial region, often associated with tingling, is the most common symptom. In patients with symptomatic trigeminal nerve dysfunction the corneal reflex is also impaired. This reflex may also be impaired in patients with large tumours with no facial sensory disturbance. Facial pain in the form of trigeminal neuralgia may result, but is relatively uncommon.

Overt weakness of the facial nerve is relatively uncommon except in very large tumours, however, up to 10 per cent of patients may experience some degree of facial twitching (Selesnick et al. 1993).

Standard treatments for acoustic neuroma

Complete surgical removal is the recommended treatment for the vast majority of acoustic neuromas (NIH Consensus Development Panel 1991; UCSF Acoustic Neuroma Team 1998). Other treatment options for management include partial surgical removal, stereotactic radiosurgery (LINAC or gamma knife) and observation.

There are three major surgical approaches commonly used: sub-occipital, translabyrithine, and middle fossa. These surgical approaches will not be discussed in detail within this review, it is sufficient to note that each has specific advantages and disadvantages (NIH Consensus Development Panel 1991). The NIH has recommended that the criteria for selecting the approach 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).

It has been suggested that the choice of approach is less important in determining outcome than the microsurgical skills of the surgeons (UCSF Acoustic Neuroma Team 1998).

Neurofibromatosis-2 patients

While hearing preservation is important for any patient with an acoustic neuroma, it is crucial for patients with NF-2, because of the likelihood of bilateral involvement.

Hearing preservation results are also generally worse in NF-2 associated tumours compared to sporadic unilateral tumours (Glasscock et al. 1992). While the available options for treating NF-2 tumours are the same as those for sporadic tumours, the criteria used to assess patient suitability for surgery are likely to be different. The decision as to whether to attempt hearing preservation surgery may be influenced by the size of tumour, degree of contralateral ear disease, and the extent of useful hearing in both ears. Advanced age is generally not a factor in deciding on surgical intervention (as can happen with sporadic tumours), as patients with bilateral tumours are usually young. Indeed, due to the earlier age of presentation and the progressive nature of the disease, adverse effects of treatment and consequences of natural history of the disease should be carefully considered (Glasscock et al. 1992).

Existing reviews

A number of previous reviews have examined the available evidence for stereotactic radiosurgery treatment of acoustic neuroma. They include:

- Health Council of the Netherlands, October 1994
- Minnesota Health Care Commission, Health Technology Advisory Committee, June 1995
- University HealthSystem Consortium Technology Assessment Program of the Clinical Practice Advancement Center, September 1995
- ECRI, February 1996
- Alberta Heritage Foundation for Medical Research, July 1999

The outcomes of these reviews are summarised in Table 21.

Table 21 Conclusions of previous health technology assessments on treatment of acoustic neuroma with stereotactic radiosurgery

Agency	Conclusions
Health Council of the Netherlands, October 1994	SRS should, in general, be viewed at present as an emerging technology that has gone beyond the experimental stage. It is often used as an adjunct to neurosurgical interventions. Surgery and microsurgery, as well as conventional external beam radiotherapy remain the principal forms of treatment for intracranial disorders. SRS for acoustic neuroma would primarily seem to be useful when microsurgical intervention involves large risks. This may be the case with older patients, patients with bilateral tumours or patients with recurrent tumours after surgery. There is a preference for SRS in the treatment of bilateral tumours (NF-2) because of the possibility of preserving residual hearing. For the application of SRS in a routine clinical setting, both the gamma knife and LINAC can be considered suitable, when looking at the quality and financial aspects. It is still too early to decide whether SRS is more effective that 'standard' treatment modalities.
Minnesota Health Care Commission, Health Technology Advisory Committee, June 1995	There is insufficient evidence regarding the clinical superiority of gamma knife versus LINAC SRS. Conventional surgery is still indicated in young, healthy patients with acoustic neuroma.
University Health Consortium Technology Assessment Program of the Clinical Practice Advancement Center, September 1995	Surgical resection is the standard therapy for acoustic neuroma. SRS with a gamma knife or LINAC is a safe alternative for selected patients. Eligible SRS patients include those who are elderly, who have a tumour in a high-risk or inoperable location, those with residual tumour after resection, those with medical comorbidities, and patients who refuse open resection. Experience with SRS in treating acoustic neuroma suggest this approach is relatively safe and effective in comparison with surgical resection in selected patients. Additional data from RCTs in larger numbers of cases are required to establish the role of SRS, especially in regard to the use of LINAC versus gamma knife procedures as well as selection criteria for using this approach rather than microsurgery. gamma knife and LINAC can be used to treat the same indications. There are no clinically proven differences in the outcomes in studies treating similar indications. Available clinical literature contains no evidence that conclusively shows a difference in the safety and efficacy of SRS performed with a gamma knife versus a LINAC.
ECRI, February 1996 (a, b)	There is no evidence that one SRS method is superior to the other. SRS for acoustic neuroma provides high rates of short-term tumour control. There are no long-term studies. It is not possible to determine whether SRS prevents tumour recurrence. Poor study methodology makes it impossible to prove that SRS preserves hearing in the affected ear more often than conventional surgery.
Alberta Heritage Foundation for Medical Research, July 1999	Microsurgery is the primary treatment option for acoustic neuroma, and surgical techniques continue to evolve. There is some evidence, from methodologically weak studies, that SRS is efficacious in treating acoustic neuroma in suitably selected individuals. Evidence on the comparative effectiveness of SRS and microsurgery remains limited. There is no evidence of any difference in effectiveness between the LINAC and gamma knife approaches to SRS. The overall performance of SRS will depend on the expertise of the patient management team and the quality of imaging and treatment planning, rather than the method used to deliver radiation.

Source: (Schneider and Hailey 1999) Alberta Heritage Foundation for Medical Research

Literature review

Search strategy

The search strategy on page 6 was combined with the following MeSH terms for Medline, PreMedline and HealthSTAR, and was conducted for 1990 to March 2000:

- 'Neuroma, acoustic' (exploded) or 'acoustic neuroma' as a key word.
- Embase was searched using the equivalent terms of 'acoustic neurinoma' (exploded) or 'acoustic neuroma' as a key word.

Microsurgery publications

Microsurgical series which were published during the same time as the radiosurgical series (1990 to March 2000) were identified by searching the above databases. The

disease-specific terms used for radiosurgery searches were also used and were combined with the terms 'microsurgery (MeSH) or surgery (MeSH) or neurosurgery(MeSH)'. Forty-nine citations (including 13 duplicates) were retrieved, and the eligibility criteria below were applied. The majority of papers were excluded as they presented results on radiosurgical rather than surgical management of acoustic neuroma. Ten surgical series were identified where primary clinical results were reported and all have been used in this review. Samii and Matthies have published a number of papers (Samii and Matthies 1997a; Samii and Matthies 1997b) including the same patient data set. Each paper presents different information: complications and facial nerve function and hearing preservation, respectively. Koos et al. (Koos et al. 1995; Koos et al. 1998) have also published two papers, with the later paper containing additional information on a subset of patients reported on in the earlier publication.

In addition, articles were also retrieved to provide background information about stereotactic radiosurgery and acoustic neuroma natural history and therapy.

Eligibility of studies

A total of 292 abstracts were identified in the literature search, of which 93 were duplicate records retrieved from different databases. The 199 non-duplicate abstracts were evaluated to exclude those definitely not eligible. The criteria below were applied to each abstract. The full article was retrieved for the 76 abstracts which were either potentially eligible or eligible, or for which there was insufficient information available in the abstract to assess eligibility.

Eligibility criteria

- Studies examining the effectiveness of stereotactic radiosurgery treatment of acoustic neuroma.
- English language journal articles reporting primary data obtained in a clinical setting (that is, reviews not included).
- Study design and methods clearly described.
  - Case series of ≥ 10 patients where the authors had attempted to address bias, for example consecutive patients, or where patients could be assumed to be consecutive (that is, all patients within a stated time period).
  - Studies with a more powerful design than case series.
- Published 1990 or later, to reflect the current status of diagnostic imaging and treatment technologies.
- Or where these inclusion criteria could not be established from the abstract.

The 76 retrieved papers were re-examined using the above criteria, and a further 57 were excluded for the following reasons:

- Clinical effectiveness of radiosurgery was not addressed by the paper (for example, treatment reviews, modelling etc)
- No attempt had been made to address selection bias in case series by using consecutive patients, that is, patients appeared to have been selected from a larger patient group, or where this criteria was still unclear from examination of the full paper.
- < 10 patients.

- Studies had been superseded by another publication using the same patient group, with the same purpose (see below).
- Studies were excluded if the patients reported on were a subset of a larger group reported in another publication.

The issue of multiple publications from the same treatment facility became a complex issue when evaluating and assessing available evidence for this indication. A large number of publications, using the same or predominantly the same patient groups have been generated from a small number of treatment centres. Only studies that were not superseded by a later publication, or did not include subsets of patients reported on elsewhere were included in the review. Thirteen publications were excluded as they had been superseded by more recent or more comprehensive publications of the same patient group. Any earlier publications that provided more comprehensive information than a later publication remain in the tables.

Nineteen radiosurgery studies have been used as the basis for this review: 11 used gamma knife technology (Table 40), three used LINAC radiosurgery (Table 41) and another five used fractionated radiosurgery (predominantly LINAC) (Table 42).

Outcomes

Before conducting the literature review, it was determined that the following outcomes be addressed, if available in the literature. The majority of papers report local control, hearing preservation and cranial nerve abnormalities, however, few provide an indication of procedural-related morbidity, such as oedema or radiation necrosis.

Table 22 Outcomes for evaluation in the review

1. Local control
2. Hearing
3. Cranial nerve abnormality
4. Other complications, eg oedema or haemorrhage

The measurement of these outcomes varied between studies. Local control, although not defined in many of the papers, is usually understood to mean regression or stabilisation of tumour growth, and can be determined radiographically (generally MRI or CT) or assessed clinically. Hearing was often assessed in radiosurgery publications using the Gardner–Robertson (GR) scale of hearing classification which assesses tonal loss (dB) and speech discrimination ability (Gardner and Robertson 1988). In microsurgery publications, however, this scale was often not used. Instead, hearing preservation was assessed using a number of other audiometric scales. All scales used to assess hearing are presented in Appendix D – Hearing Classification Scales.

Cranial nerve function predominantly involved assessing facial nerve function, and trigeminal nerve function. Facial nerve function was often assessed using the House–Brackmann scale (Table 23) which involves a clinical assessment of facial nerve paralysis (House and Brackmann 1985). This scale was used fairly consistently across both radiosurgery and microsurgery publications. Authors of radiosurgery publications sometimes provided an assessment of trigeminal nerve function, generally using subjective assessment of pain, loss of sensation and functional impairment before and after procedures were used. Microsurgery publications did not assess trigeminal nerve function.

Table 23 House–Brackmann scale for facial nerve function

Functional grade	Symptoms
1.	Normal in all areas
2.	Mild dysfunction (slight weakness on close inspection, complete eye closure)
3.	Moderate dysfunction (obvious but not disfiguring difference between two sides; forehead shows slight to moderate movement; complete eye closure with effort)
4.	Moderately severe dysfunction (obvious weakness or disfiguring asymmetry; no forehead movement; incomplete eye closure)
5.	Severe dysfunction (barely perceptible motion)
6.	Total paralysis

Results

Is it safe?

Safety outcomes were particularly difficult to evaluate in this review. Papers often did not report information in a consistent manner, and it was often not possible to determine at what point after treatment the complications developed or were reported, thereby limiting comparison across studies. As discussed above, the safety outcomes of interest can be categorised into three broad areas: cranial nerve abnormalities, hearing preservation, and procedural morbidity and mortality. It is important to note that the methodological limitations of all studies (microsurgical and radiosurgical) and the small sample sizes limit the usefulness and clinical applicability of any information presented here (Rowed and Nedzelski 1997; Samii and Matthies 1997a).

Cranial nerve abnormalities (trigeminal and facial neuropathies)

Authors reported results in a number of different manners, making it difficult to compare across studies. Some authors reported incidence rates (crude or actuarial) of new or worsening neuropathies, other authors reported only the incidence of new neuropathies, and some reported only worsening of pre-existing conditions or did not state which outcome the reported rates represented. To complicate the assessment of safety further, authors rarely reported whether the neuropathies were permanent or transient and, with the exception of two papers (Flickinger et al. 1996b; Miller et al. 1999) did not indicate when after treatment the complications were assessed.

Trigeminal neuropathy appeared to affect approximately 3–30 per cent of patients treated with gamma knife radiosurgery, approximately 12–18 per cent of patients treated with LINAC radiosurgery and approximately 0–16 per cent of patients treated with fractionated radiosurgery. Facial neuropathies appeared to affect between 8 per cent and 50 per cent of patients treated with gamma knife radiosurgery, approximately 8–24 per cent of patients treated with LINAC radiosurgery and up to 5 per cent of patients treated with fractionated radiosurgery. This seems lower than that with gamma knife and LINAC, however, it is impossible to determine whether the method of irradiation determines safety. Given the small numbers and poor methodology in all of these series, caution should be used when interpreting these results.

Microsurgery publications did not report incidence of trigeminal neuropathies. Facial neuropathies appeared to affect between 10 per cent and 50 per cent of patients. The incidence appeared to be greater immediately after surgery, and decreased with time after surgery to approximately 10–20 per cent at 12–18 months after surgery. Although not reported in Table 24 below, many authors of the microsurgery series report good success with surgical re-inervation of those nerves severed during the microsurgical removal of the tumour.

Table 24 Cranial nerve abnormalities resulting from treatment of acoustic neuroma

		Trigeminal neuropathy				Facial neuropathy			
Study	**N Patients (tumours)**	**New or exacerbation (%)**	**New only(%)**	**Exacerbation only (%)**	**Assessment method not defined (%)**	**New or exacerbation (%)**	**New only (%)**	**Exacerbation only (%)**	**Assessment method not defined (%)**
Microsurgery									
(Guerin et al. 1999)	611 (?) 536 evaluated at 1yr	nr	nr	nr	nr	10.2% @ 1 yr had H-B grade 3-6 (mod to severe dysfunction)			
(Irving et al. 1998)	98 (100) 91 @1yr	nr	nr	nr	nr	Post-op: 50% @1yr: 18/91: 20%			
(Koos et al. 1995)	364 (?) Anatomical preserved Overall: n=351/365 Small n=85/87 Large n=266/277	nr	nr	nr	nr	Overall: 1 week post op: 14% with any dysfunction 12-18 months: 7% with any dysfunction Small: 12% (10/85) with any dysfunction Large: 15% (40/266) with any dysfunction			
(Koos et al. 1998)	452 (?) Anatomical preserved Small n=113/115	nr	nr	nr	nr				14 16/113
(Samii and Matthies 1997a)	962 (1000)	nr	nr	nr	nr				Post-op 53
(Gormley et al. 1997)	179 (?) 173 evaluable	nr	nr	nr	nr	23 (40/173)			
Gamma knife radiosurgery									
(Miller et al. 1999)	82	21				23			
(Walch et al. 1999)	79		3				8		
(Vermeulen et al. 1998)	52 (54)		7				20		
(Kwon et al. 1998)	88				3				8
(Kondziolka et al. 1998)	162		16[1]				15[1]		
(Ito et al. 1997)	46	30				50			
(Flickinger et al. 1996b)	273	18				14			
(Forster et al. 1996)	27 (29)		20[1]				38[1]		
(Kobayashi et al. 1994)	40 (44)	7				16			
(Noren et al. 1993)	(254)	19				17			
LINAC radiosurgery									
(Tomasevic et al. 1998)	31 (34)	18				24			
(Valentino and Raimondi 1995)	23 (24)			13				8	
Fractionated radiosurgery									
(Poen et al. 1999)	33 (34)	16				3			
(Shirato et al. 1999)	50		12 transient				5 transient		
(Lederman et al. 1997)	38 (39)		0				3		
(Varlotto et al. 1996)	12		0				0		
(Andrews et al. 1995)	26 (27)		13				0		

[1] percentage of patients with previously normal function

NR – not reported by authors

Note: information from the case series, there has been no adjustment or weighting for sample size. As many papers present results from small case series, extreme percentages should be viewed with caution

Hearing preservation

Hearing preservation is a difficult outcome to assess as the natural course of acoustic neuroma involves the progressive loss of hearing in the affected ear. Many patients, therefore, have a pre-existing hearing deficit at the time they undergo surgery, which tends to complicate the assessment of this outcome. In some patients this progressive hearing loss may continue even after treatment.

In order to evaluate auditory status it is useful to quantify hearing tests using a classification that standardises the results (Thomassin et al. 1998). The Gardner–Roberston scale is one scale that is used, and was often reported in radiosurgery publications (Gardner and Robertson 1988). Patients who had no hearing (Gardner–Robertson Grade V) at the time of treatment were generally excluded from any analysis of hearing preservation, for obvious reasons. Those patients with any hearing prior to treatment were assessed pre-treatment using the Gardner–Robertson scale to determine level of available hearing. Gardner–Robertson Grades I–II are generally grouped together to represent patients with useful or serviceable hearing before treatment (although some authors (Poen et al. 1999) report Grades I–III as serviceable hearing and Grades I–II as useful hearing). Other authors simply report 'useful hearing' with no indication of how this has been measured, or report on 'preservation of Gardner–Robertson grade', which is clinically relevant only in those patients with useful or serviceable hearing before treatment. The proportion of patients treated with radiosurgery who had useful or serviceable pre-treatment hearing ranged from 3 per cent to 75 per cent. This ranged from 10–100 per cent for patients treated with microsurgery.

Microsurgery publications frequently did not report auditory function using the Gardner–Roberston scale. They used a variety of other scales (see Appendix D – Hearing Classification Scales: AAO-HNS (American Academy of Otolaryngology - Head and Neck Surgery 1995), Norstadt scale and Hannover scale (Samii and Matthies 1997b) and the Shelton classification (Shelton C. and Hitselberger 1991)), or did not report on how hearing was assessed and categorised. Where radiosurgery series often reported hearing preservation rates in patients with useful pre-treatment hearing, microsurgery publications frequently reported anatomical preservation of the nerve and any hearing preservation. The fact that a consistent and standardised measure was not used limits the comparison of hearing preservation rates between the microsurgery series. The comparison of microsurgery to radiosurgery hearing preservation rates is also markedly compromised for this reason.

The most clinically relevant hearing outcome is maintenance of useful hearing in those patients with useful pre-treatment hearing. Some authors report on this outcome, or relevant information was able to be extracted from the paper, and the results have been tabulated in Table 25.

The proportion of patients (with useful pre-treatment hearing) treated with radiosurgery who maintained useful post-treatment hearing ranged from approximately 20 per cent to 100 per cent. Most studies reported preservation rates of approximately 60–70 per cent of those patients with useful pre-treatment hearing. This proportion of patients did not appear to differ greatly between treatment methods. As only three papers (Forster et al. 1996; Thomassin et al. 1998; Miller et al. 1999) report hearing preservation rates at a specific time after treatment, it is impossible to distinguish whether we are comparing rates within a comparable timeframe. It is also important to note that in some studies only a proportion of patients with pre-treatment audiological assessment actually underwent audiometry after treatment, thereby overestimating the actual hearing

preservation rate (as the denominator of available patients is considerably reduced). These factors, coupled with the small patient numbers and less than ideal methodology, precludes any definitive comparison of hearing preservation rates between radiosurgical treatment methods.

Table 25 Hearing preservation in patients with useful pretreatment hearing

Study	Hearing scale used[1]	Total N Patients (tumours)	Patients with pre- and post-treatment audiological assessment		Useful/serviceable (G-R I-II or equivalent) pretreatment hearing		Preserved useful hearing after treatment	
			N	% total patients	N	% patients with audiology (if avail.) or total	N	% patients with useful baseline hearing
Microsurgery								
(Irving et al. 1998)	AAO–HNS	98 (100)	49/100	49	48/49	98	33/49	67
(Koos et al. 1995) Overall	NR	364	NR	NR	129/364	35	95/129	74
Small tumours		87	NR	NR	79/87	91	68/79	86
Large tumours		277	NR	NR	50/277	18	27/50	54
(Koos et al. 1998) Small only	NR	115	NR	NR	101/115	88	90/101	89
(Samii and Matthies 1997b)	Norstadt Hannover	962 (1,000)	NR	NR	507/1,000	51	144/507	28
(Hecht et al. 1997)	G–R Shelton	60	NR	NR	60/60	100	16/60	27
(Gormley et al. 1997) Overall	G–R	179	NR	NR	69/179	39	26/69	38
Small tumours	G–R	67	NR	NR	42/67	63	20/42	48
Medium tumours	G–R	84	NR	NR	24/84	29	6/24	25
Large tumours	G-R	28	NR	NR	3/28	11	0/3	0
(Rowed and Nedzelski 1997)	NR	26	NR	NR	23/26	88	11/23	48
(Ramsay and Luxford 1993)	NR	65	NR	NR	NR	NR	0	0
Gamma knife radiosurgery								
(Miller et al. 1999)	G–R	82	79	96	13/79	16	One year actuarial incidence 92%. Two year actuarial incidence 39%.	
(Walch et al. 1999)	NR	79	69	87	21/69	30	14/21	67
(Thomassin et al. 1998)	G–R	138	104	75	48/104	46	10/48	21
(Kwon et al. 1998)	NR	88	NR	NR	3/88	3	2/3	67
(Kondziolka et al. 1998)	G–R	162	NR	NR	32/162	20	15/32	47
(Flickinger et al. 1996b)	G–R	273	NR	NR	63/273	23	38/63	60
(Forster et al. 1996)	G–R	27	NR	NR	18/27	67	9/18	50
Fractionated radiosurgery								
(Poen et al. 1999)	G–R	33	NR	NR	13/33	39	10/13	77
(Varlotto et al. 1996)	NR	12	NR	NR	9/12	75	9/9	100
(Andrews et al. 1995)	NR	26	NR	NR	7/26	27	5/7	71

[1] Hearing classification scales reported in Appendix 1

G–R – Gardner–Robertson scale (Gardner and Robertson 1988)

AAO–HNS – American Academy of Otolaryngology – Head and Neck Surgery guidelines (American Academy of Otolaryngology - Head and Neck Surgery 1995)

Norstadt – Norstadt Hearing classification system (Samii and Matthies 1997b)

Hannover – Hannover Hearing classification system (Samii and Matthies 1997b)

Shelton – Shelton hearing classification system (Shelton C. and Hitselberger 1991)

NR – not reported by authors

Note: no papers using LINAC radiosurgery reported hearing outcomes in a manner comparable to other papers therefore they have not been included here

Microsurgical resection of acoustic neuroma resulted in hearing preservation rates of between zero and 90 per cent in patients with useful pre-treatment hearing. The proportion of patients who maintained this level of functional hearing appeared to be

dependent on the size of the tumour with hearing preservation improved in patients with smaller tumours (Koos et al. 1995; Gormley et al. 1997). The rates of hearing preservation in patients treated with microsurgery appear to be quite similar to those reported for all three radiosurgery treatments, particularly in patients with small tumours.

Other treatment-related complications

Very few radiosurgery papers actually reported other treatment-related complications, such as radionecrosis, oedema or haemorrhage. Only eight of the 19 included radiosurgery papers reported on other treatment-related complications. It was also noted during the review, that radiosurgical series were also very unlikely to provide information on the mortality of patients. It is unclear whether this is because no patients died, or whether the authors simply did not report it. The results from these papers are tabulated in Table 26.

Microsurgical complications predominantly consisted of infection and cerebrospinal fluid (CSF) leak, and authors also provided information regarding patient mortality. Procedural-related mortality appeared to be less than 1 per cent, with CSF leak being the most common treatment-related morbidity, with approximately 10–25 per cent of patients developing a CSF leak or fistula. It should be noted that only a very small percentage of these patients actually required surgical intervention with shunt insertion to correct the problem. Meningitis was reported in about 2–3 per cent of patients and resolved with antibiotics. The details are summarised in Table 26.

Table 26 Other treatment–related complications

	Complications (% patients)														
Study	N	Death (procedural related)	Haemorrhage	Oedema	CSF leak or fistula	CSF leak needing surgery	Hydrocephalus (shunt not needed or not reported)	Hydrocephalus needing shunt insertion	Meningitis	Nausea/vomiting	Ataxia	Wound infection	Hemiparesis	Other nerve palsy	Surgical intervention needed
Microsurgery															
(Guerin et al. 1999)	611	<1	<1		25	1			2						1
(Samii and Matthies 1997a)	962	1	2		9		1	1	3			<1	<1		
(Gormley et al. 1997)	179	1			15	2		3	3		1	2		2	
(Ramsay and Luxford 1993)	65	0			11	5			2						
Gamma knife radiosurgery															
(Miller et al. 1999)	82							1							
(Kwon et al. 1998)	88							3		1					
(Kondziolka et al. 1998)	162							2			4				
(Kobayashi et al. 1994)	44			5				5							
(Noren et al. 1993)	254			8				3							
LINAC radiosurgery															
(Tomasevic et al. 1998)	31						3								
(Mendenhall et al. 1996)	56						5								
Fractionated radiosurgery															
(Andrews et al. 1995)	26						8			8	15				

Is it effective?

The reviewers were unable to identify any studies where a control group was available, including randomised trials, cohort studies or case control studies. The highest level of evidence available was therefore case series (NHMRC Level IV evidence).

In the absence of a randomised controlled trial comparing microsurgical resection to radiosurgery, it is difficult to compare the true efficacy of these two treatment modalities for similar cases. This difficulty is exacerbated by problems with selection bias for both treatment options, and the fact that surgical series report tumour **resection** rates and radiosurgical series report tumour **control** rates. Rapid changes in surgical and radiosurgical techniques can also complicate longitudinal comparison of patient outcomes (Rowed and Nedzelski 1997; Samii and Matthies 1997b) Schneider and Hailey (1999) have also questioned the validity and reliability of combining and comparing results from different treatment centres, given the variation in expertise, patient selection and treatment protocols across sites. This applies equally to microsurgery and radiosurgery treatment centres.

As can be seen from Table 27, the rates of complete microsurgical resection of acoustic neuroma were very high, with only a small proportion of tumours recurring. Not all surgical papers reported resection rates, as it is generally assumed that the tumours are completely resected. Only those reporting this information have been included in Table 27.

Table 27 Microsurgical resection of acoustic neuroma

Study	Years	N (patients/ tumours)	Complete resection		Deliberate partial resection		Non-deliberate partial resection		Recurrence		Comments
			N	%	N	%	N	%	N	%	
(Guerin et al. 1999)	1973–94	611/?	610/611	100	1/611	<1	0	0	5/611 @ 5yrs	< 1 @ 5yrs	
(Samii and Matthies 1997a)	1978–93	962/1000	979/1000	98	21/1000	2	0	0	7/880	1	880 non NF-2 tumours, unclear timeframe after original surgery
(Gormley et al. 1997)	7/1985–6/1996	179/?	178/179	99	1/179	<1	0	0	NR	NR	Deliberate partial resection in NF-2 patient to preserve hearing
(Ramsay and Luxford 1993)	1982–89	65/65	61/65	94	4/65	6	0	0	NR	NR	Elderly patients (> 70) only

NR – not reported by authors

Where microsurgery papers report on complete resection rates, control of tumour growth is the aim of treatment with microsurgery. As such, radiosurgery series report the proportions of patients who achieve control (stability or regression of tumour growth) and those whose tumours progress.

It should be noted that in the table above Kondziolka et al (1998) reported fewer progressions in year three than in year two. Intuitively this does not appear possible, however the authors have explained this anomaly by suggesting that the 5 per cent of patients at year two actually included five patients who appeared to progress due to expansion of tumour margins as the central portion of the tumour became necrotic.

Reported rates of tumour control (that is, those achieving regression or stability of tumour growth) ranged from approximately 80–100 per cent. Again, due to the small patient numbers and the uncontrolled nature of patient selection, these percentages should be interpreted with caution. It is also often not clear from the papers when tumour control rates are measured. Comparison of control rates between series is therefore difficult.

Few papers report on the number of patients treated with radiosurgery who require subsequent microsurgical removal of their tumours. Four papers from the 19 included in this report contain this information (Valentino and Raimondi 1995; Kwon et al. 1998; Shirato et al. 1999; Miller et al. 1999) and rates ranged between 2 per cent and 8 per cent of patients. Previously discussed methodological issues limit comparison.

Table 28 Radiosurgery tumour control rates

Study	N Patients (tumours)	Patients with radiographic imaging		Tumour control rate (regression or stable)		Regression		Stable		Progression		Needing subsequent surgery	
		N	%	N	%	N	%	N	%	N	%	N	%
Gamma knife radiosurgery													
(Miller et al. 1999)	82	78/82	95	75/78	96	–	–	–	–	3/78	4	2/78	3
(Walch et al. 1999)	79	NR	NR	79/79	100	8/79	10	71/79	90	0	0	NR	NR
(Vermeulen et al. 1998)	52 (54)	42/52	81	38/42	90	–	–	–	–	4/42	10	NR	NR
(Kwon et al. 1998)	88	63/88	72	60/63	95	33/63	52	27/63	43	3/63	5	2/88	2
(Kondziolka et al. 1998)	162	NR	NR				1yr 25 2yr 47 3yr 59		1yr 74 2yr 48 3yr 38		1yr 1 2yr 5 3yr 3	NR	NR
(Ito et al. 1997)	46	NR	NR	44/46	96%	10/46	22%	34/46	74%	2/46	4	NR	NR
(Flickinger et al. 1996b)	273 (273)	NR	NR	7 yr actuarial clinical control rate 96% 7 yr actuarial radiological control rate 91%		–	–	–	–	7yr actuarial progression rate (not req. surgery) 5%			
(Forster et al. 1996)	27 (29)	NR	NR	23/29	79%	6/29	21%	17/29	58%	6/29	21%	NR	NR
(Noren et al. 1993)	(254) 61 NF-2	NR	NR				Unilat 55% Bilat 33%		Unilat. 33% Bilat. 43%		Unilat 12% Bilat 24%	NR	NR
LINAC radiosurgery													
(Tomasevic et al. 1998)	31 (34)	27/34	79			3/27 > 50% ↓ size	11	22/27	81 0–50% ↓ size	NR	NR	NR	NR
(Mendenhall et al. 1996)	56	27/56 @ 2yrs	48 @ 2 yrs	27/27	100	19/27	70	8/27	30	0	0	NR	NR
(Valentino and Raimondi 1995)	23 (24)	23/23 @ 2yrs	100 @ 2 yrs	23/24	96	9/24	38	14/24	58	1/24	4	2/24	8
Fractionated radiosurgery													
(Poen et al. 1999)	33 (34)	32/34	91	2 year actuarial freedom from progression 93%		11/32	34	20/32	63	1/32	3	NR	
(Shirato et al. 1999)	50	NR	NR	42/50	84	–	–	–	–	8/50	16	1/50	2
(Lederman et al. 1997)	38 (39)	NR	NR	39/39	100	26/38	68	12/38	32	0	0	NR	NR
(Varlotto et al. 1996)	12	12/12	100	12/12	100	3/12	25	9/12	75	0	0	NR	NR
(Andrews et al. 1995)	26 (27)	NR	NR	Control of all evaluable tumours		NR	NR	NR	NR	NR	NR	NR	NR

Conclusions

There is limited, high quality information on the safety and effectiveness of different treatments for acoustic neuroma and no reliable data comparing approaches.

Microsurgical resection is the recommended treatment of choice for patients with acoustic neuromas who are fit for surgery, and particularly for those with small unilateral tumours.

Microsurgery appears to offer complete resection rates of close to 100 per cent (in patients selected for surgery), facial nerve complication rates of up to 20 per cent at one year, and useful hearing preservation rates of between 30 per cent and 90 per cent. Outcomes are likely to depend on the skills of the surgeons.

Reported results of radiosurgical interventions are similar to microsurgery with tumour control rates of close to 100 per cent and with facial nerve complication rates and useful hearing preservation rates similar to those reported for microsurgery.

There appears to be little difference in these parameters between gamma knife and LINAC radiosurgery, although there is a suggestion that fractionated radiosurgery may cause fewer cranial nerve complications.

Outcomes of patients with neurofibromatosis-2-associated acoustic neuroma were not specifically examined in this review.

Changes in methods over time complicate longitudinal comparisons of radiosurgery and microsurgery.

Radiosurgery may be effective treatment for selected groups of patients, for example those with surgically inaccessible lesions and those with comorbidities which preclude surgical intervention.

The quality and quantity of evidence on the effectiveness and safety of stereotactic radiosurgery and microsurgery is, however, limited. The current information does not allow reliable comparison of treatments and it is therefore not possible to determine whether one method is superior to any other.

It is likely that the outcomes will depend more on the treatment team expertise, quality of imaging and treatment planning than on the method used to deliver the radiation or the surgical approach.

What are the economic considerations?

Summary of findings

As the issues of effectiveness and safety are yet to be conclusively determined, it is not possible to perform a true economic evaluation of the role of gamma knife radiosurgery or comparators in the management of patients with arteriovenous malformations, brain metastases and acoustic neuroma.

While a number of 'partial economic analyses' from overseas have been published, the results of these analyses are not directly applicable to the Australian healthcare environment. Differences in unit costs, treatment patterns, resource utilisation and reimbursement systems between Australia and other countries limits our ability to generalise overseas results to Australia.

As the currently available evidence does not allow definitive conclusions regarding the comparative effectiveness and safety of gamma knife to other treatment alternatives, a formal cost-effectiveness analysis cannot be conducted.

Equipment cost per treatment with gamma knife ranged from $4,188 to $20,581 and for LINAC ranged from $1,614 to $11,607 over a range of scenarios. The cost ratio of gamma knife equipment costs per treatment to LINAC equipment costs per treatment ranged from 1.7–2.9, that is, gamma knife was consistently 1.7 to 2.9 times more expensive than LINAC depending on the costing scenario examined.

Estimates of equipment cost per treatment depend on the upfront capital acquisition costs, the useful life of the equipment and the number of treatments per year.

Average direct medical costs are based on AN-DRG (Australian National Diagnosis Related Groups) estimates and do not differentiate between indications. Average AN-DRG costs may over or under-estimate true treatment costs for a specific indication.

A comprehensive Australian-based assessment of clinical effectiveness and costs is needed if more accurate estimates of these parameters and a comparison between treatment alternatives are required.

Published economic evaluations

While this report presents some information regarding the efficacy of radiosurgery, there is insufficient published evidence from which to conclude definitively that gamma knife radiosurgery is equivalent to LINAC radiosurgery or that either are equivalent to or better than standard care. It should be noted that **evidence of no difference in effect** (as would be required to perform a true economic evaluation) is not the same as **no evidence of a difference in effect** (as we have within this review).

As the issues of effectiveness and safety are yet to be conclusively determined, it is not possible to perform a true economic evaluation of the role of gamma knife radiosurgery in the management of patients with arteriovenous malformations, brain metastases and acoustic neuroma. Despite this, a number of published 'economic analyses' were located in the literature databases.

The search strategy on page 6 was combined with the following MeSH terms for Medline, PreMedline and HealthSTAR, and was conducted for the period 1990 to March 2000.

- 'Costs and cost analysis' (exploded) or 'cost effect$' as a key word
- Embase was searched using the equivalent terms of 'cost' (exploded) or 'cost benefit analysis' (exploded) or 'cost control' (exploded) or 'cost effectiveness' (exploded) or 'economics' (exploded).

As discussed previously, the NHS Centre for Reviews and Dissemination databases (DARE, EED and HTA) were also searched.

Of the 109 papers found, the large majority were not economic evaluations but review papers which mentioned costs of treatment. Seven papers were identified which could be described as descriptive or partial economic evaluations (Table 29). None of these studies were conducted in Australia, and therefore any costings and results are not directly applicable to the Australian healthcare environment.

Table 29 Costing and economic analyses of radiosurgery

Reference	Country	Indication	Brief results
(Becker et al. 1998)	Germany	Costing only (abstract only)	Compared modified LINAC, dedicated LINAC and gamma knife. Costs included capital, installation, annual service, repair, quality control, personnel etc. Volume-dependent costs calculated. • Total acquisition costs modified LINAC (850,000DM) < dedicated LINAC (3,500,000 DM) < gamma knife (6,300,000 DM). • Total annual costs modified LINAC (137,00 DM) < dedicated LINAC (787,500 DM) < gamma knife (1,118,500 DM). For ≤ 200 patients the modified LINAC had the lowest cost per treatment.
(Konigsmaier et al. 1998)	Austria	Costing only	Compared modified LINAC, dedicated LINAC and gamma knife. Costs included investment costs, operating costs and staffing costs. For ≤ 175 patients the modified LINAC cost 6345 DM per patient. For > 200 patients authors report gamma knife was less costly than dedicated LINAC, but do not provide estimate of cost per treatment for > 200 patients for the modified LINAC.
(Ott 1996)	United States	Costing only	Compared actual hospital charges for craniotomy and surgery (for different diagnoses) with nominal gamma knife costs. Only a proportion of patients would have been eligible for gamma knife radiosurgery: in these patients gamma knife cost US$22,000 and surgical treatment cost US$25,149. NB: gamma knife fees only includes the gamma knife service fee, with no subsequent follow-up care, hospital costs include costs for treatment of AEs and complications.
(Porter et al. 1997)	Canada	AVMs	Cost utility analysis using a decision tree model comparing LINAC radiosurgery to surgery for small operable AVMs. Surgery conferred a 0.98 QALY benefit at an additional cost of CDN$6,937 with an incremental cost-utility ratio of CDN$7,100 per QALY for patients treated surgically. Authors concluded surgical benefit was mainly related to earlier and more successful protection from haemorrhage for patients treated surgically.
(Rutigliano et al. 1995)	United States	Cerebral metastases	Cost effectiveness for surgery plus WBRT compared to radiosurgery (gamma knife) plus WBRT for patients with a single brain metastasis. WBRT used for incremental analyses. Outcomes from published literature – Life years saved (LYS) estimated from median survival. Cost effectiveness ratio was US$3,2149 per LYS for surgery plus WBRT; US$2,4811 for radiosurgery plus WBRT. Incremental cost-effectiveness ratio for surgery plus WBRT was US$52,384 per additional LY over WBRT alone; and for radiosurgery plus WBRT was US$4,0648 per additional LY over WBRT alone. Authors advocate need for prospective trials to examine clinical and cost effectiveness of surgery and radiosurgery in management of a single metastasis.

(Mehta et al. 1997)	United States	Cerebral metastases	Cost effectiveness and cost utility analysis comparing WBRT alone with surgery plus WBRT and radiosurgery (RS) (LINAC) + WBRT for patients with a single brain metastasis. LYS estimated from literature by median survival; QALYs estimated from literature by median duration patient capable of independent living (KPS>70). WBRT alone cost US$16,250 per LYS and US$32,500 per QALY; surgery plus WBRT cost US$27,523 per LYS and US$31,454 per QALY; RS + WBRT cost US$13,729 per LYS and US$15,102 per QALY. Incremental cost-effectiveness ratio for RS + WBRT over WBRT alone US$12,289 per LYS. Incremental cost-utility ratio for RS + WBRT over WBRT alone US$10,753 per QALY. NB: QALY measure based on functionality not quality therefore is not a true indicator of QOL
(van Roijen et al. 1997)	Microsurgery: Netherlands Gamma knife radiosurgery: Sweden	Acoustic neuroma	Comparison of costs and effects of microsurgery and radiosurgery (gamma knife) in treating acoustic neuroma; costs included direct and indirect (costs + QOL estimated from HLQ; SF-36 and EuroQOL). NB: cost and effect estimates for microsurgery was based on Netherlands data. NB: cost and effect estimates for radiosurgery was based on Swedish data. Costs of radiosurgery assumed > 200 patients per year. Clinical outcomes between treatments were similar. Direct costs for microsurgery were Dfl 20,072; for radiosurgery: Dfl 14,272. Indirect costs for microsurgery were Dfl 16,400; for radiosurgery Dfl 1,020 mainly due to time absent from work. NB: social security system of Netherlands and Sweden differ markedly with Netherlands offering attractive length and level of benefits and Sweden actively discouraging incapacity from work. Indirect costs may therefore be inaccurate. Average direct costs per RS treatment was heavily dependent upon number of treatments per year; at < 100 patients per year radiosurgery direct costs exceeded those of microsurgery.

It should be noted that overseas economic analyses cannot be applied directly to the Australian health system because of major differences in overseas patterns of health resource utilisation and unit costs compared to Australia. Managed care arrangements, such as those in the United States, also preclude any direct application of overseas results to Australia. It is relevant, however, that many evaluations indicate that the number of radiosurgery treatments per year is a critical variable for determining the relative cost of treatment options.

Commentary on the economic component of the gamma knife MSAC submission

In the absence of demonstrable equivalence or superiority of gamma knife and its comparators, we have counted the costs of a gamma knife facility. Table 30 indicates the costs that an applicant must provide in a MSAC submission. The applicant must provide these costs and their respective sources for the proposed service and comparators. Unfortunately, the applicant provided only a limited amount of this information, and sources of costs were rarely provided. For this reason, any costing, staffing and utilisation estimates provided in the application has been interpreted with caution.

The application uses an exchange rate of 0.66 to convert United States dollars to Australian dollars for all costs. This may be an overly simple method of determining true Australian costs and it is likely that these costs do not represent the true landed costs of acquiring a gamma knife machine for Australia, or the true costs (for example, staffing, maintenance) of running a gamma knife facility. There are, in addition, inconsistencies in the actual information reported (for example, estimated life of radiosurgery equipment).

Table 30 Cost information required for MSAC applications

Item
Major capital equipment:
• purchase price
• estimated life of equipment
• cost of borrowing
• annual maintenance costs
• estimated volumes per annum
Equipment cost per examination or treatment
Direct treatment costs:
• proposed professional fee
• cost of associated medical services
• cost of associated diagnostic and investigational services
• cost of hospital services
• cost of community based health services
• any other costs
Indirect or societal costs:
• cost of patient time in treatment or recovery
• costs of informal care

Source: (Commonwealth Department of Health and Aged Care 2000b).

Major capital equipment

The following major capital equipment and maintenance cost estimates (Table 31) come from the application, and from an Australian LINAC radiosurgery centre (Smee 2000).

Table 31 Cost estimates and timing

	Costs from application		Estimated costs for a new dedicated LINAC radiosurgery facility (Smee 2000)	Estimated costs for converting an existing LINAC to radiosurgery capability
Item	**Gamma knife**	**LINAC**	**LINAC**	**LINAC**
Major capital equipment	**Cost (AU$)**	**Cost (AU$)**	**Costs (AU$)**	**Costs (AU$)**
Purchase	5,303,030	1,515,151	1,800,000	0
Cost of radiosurgery adaptation equipment	0	757,575 (total costs)	1,250,000 (total costs)[1]	1,250,000 (total costs)[1]
Software controller		–	200,000	200,000
Mini multileaf collimator		–	400,000	400,000
Planning equipment		–	500,000	500,000
Head and body localisation/fixation		–	150,000	150,000
Cost of quality assurance	0	75,757[2]	70,000 pa	70,000 pa
Cobalt re-load (year 7)	833,333	0	–	–
Refurbishing (year 7)	0	530,303	Not necessary	Not necessary
Replacement of radiosurgery adaptation equipment (year 6)	0	303,030	Not necessary	Not necessary
Replacement of radiosurgery adaptation equipment (year 11)	0	303,030	Not necessary	Not necessary
Cost of facility works	833,333	833,333	–	–
Estimated life of equipment (years)	14	14	14	14
Interest rate (%)	8	8	–	–
Patients per annum (assumption)	>200	>200	–	–

[1] These costs represent approximate costs for items purchased separately. It is likely that if items were purchased as a package the total cost would be considerably less than the sum of the individual components

[2] It is unclear from the applicant's submission whether this single cost is an annual, periodic or a one-off cost.

The estimated of life of equipment varies, depending upon where in the submission it is reported. The applicant's unreferenced estimates of the useful life of a gamma knife machine vary from 10–12 years. The unreferenced estimate for the useful life of a LINAC machine was seven years and five years for the radiosurgical adaptation equipment. The applicant reports that a substantial upgrade is required for the this machine at six to seven years (unreferenced), and it is assumed that this upgrade extends the useful life of the LINAC machine to 14 years, although this is not explicitly stated by the applicant.

One of the largest local LINAC radiosurgery facilities has indicated that the LINAC radiosurgery machine within their facility has been in use for 13 years without an extensive upgrade, although it is now approaching the end of its working life. Radiosurgery adaptation equipment at this facility has been in use for 10 years, and is still fully functional (Smee 2000). Estimated costs for conversion of an existing linear accelerator to have radiosurgery capabilities have also been included.

The evaluator used a sensitivity range of 10–14 years working life to calculate approximate equipment cost per treatment for both gamma knife and LINAC machines.

Separate costing scenarios for dedicated and adapted LINAC radiosurgery based on local Australian experience have been included (Tables 33 and 34)

The application provides no estimates of cost for quality assurance for the gamma knife machine. It is unclear from the submission whether the LINAC quality assurance costs of $75,757 are annual, periodic or one-off costs. The Australian estimates (Smee 2000) provide an approximate annual quality assurance and maintenance cost.

While it is likely that the gamma knife machine will have lower quality assurance costs than a LINAC machine (due to the fewer moving parts in a gamma knife), it is suggested that the committee consider whether these costs will be zero. LINAC quality assurance costs are treated as a one-off cost in Scenarios 1–3 and an annual cost in Scenarios 4 and 5 (Table 34).

The application indicates that a Cobalt-60 source reload occurs at seven years, at the same time as an 'extensive upgrade'. The applicant has included in their costs, $833,333 for a source replacement, and it is unclear whether this cost also incorporates the 'extensive upgrade'. Supporting Committee members and local experts (Smee 2000) have indicated that it is preferable to replace the Cobalt source after **five years**, rather than after seven years. Given that the gamma knife machine is unable to be used for approximately three months during the source replacement, it is likely that the 'extensive upgrade' indicated by the applicant would occur at the same time. If the upgrade is not conducted at the same time as the source replacement, then it is likely to incur an additional (unknown) cost (Smee 2000).

Different costing scenarios model Cobalt source replacement after five years and after seven years.

The application reports the cost of facility works to be $833,333 for both the gamma knife and LINAC machines. This estimate is based on US$550,000 for a 200$m^2$ gamma knife facility.

The application assumes a dedicated clinical operation with over 200 patients per year. Based on estimates of recent LINAC stereotactic radiosurgery treatment episodes in Australia, 200 patients treated per year (or 200 treatment episodes) at a single gamma knife facility may be an overestimation of the true patient load.

Recent Australian estimates of LINAC radiosurgery usage are tabulated in Table 32.

Table 32 LINAC radiosurgery treatment episodes (Australia)

Year	Number of treatment episodes	Source
1998–99	93	MBS Utilisation Data 1998–99 (Item number 15600)
1999	Approx. 400 'courses of treatment'	Dr Graeme Morgan (St Vincent's Radiation Oncology – Radiation Oncology Workforce Survey 1994–99)
1996–97	302 occurrences (combined public and private acute hospitals)	1996–97 Australian hospital morbidity data, AN-DRG v3.1 (Table 17) (http://www.health.gov.au:80/casemix/report/hospmor1.htm)
1997–98	431 occurrences (combined public and private acute hospitals)	1997–98 Australian hospital morbidity data, AN-DRG v3.1 (Table 13) (http://www.health.gov.au:80/casemix/report/hospmor1.htm)

As LINAC radiosurgery is predominantly delivered as a single fraction, it may be reasonable to assume that the number of treatment episodes is approximately equivalent to the number of patients treated.

There are currently eight functioning LINAC radiosurgery facilities in Australia (NSW, three; Victoria, two; Queensland, one; South Australia, one; Western Australia, one). As the numbers in Table 34 represent the total treatment episodes for all Australian LINAC facilities, the average number of treatment episodes per facility is about 50 – far below the estimate of 200 treatments at the gamma knife facility assumed in the submission. Although it is recognised that this is a crude estimate, and centres in larger capital cities are likely to treat a higher number of patients, a range of patient numbers has been used to provide a range of equipment costs per treatment episode. 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 (or microsurgery) at small radiosurgery patient volumes (that is, 200 or less). It is also important to recognise that a modified LINAC machine is capable of treating patients with radiotherapy when it is not being used for radiosurgery, a facility the gamma knife does not possess. From the patient number estimates above, 200 patients per year (as proposed in the gamma knife submission) may be an optimistic estimate of the likely use of a single gamma knife facility in one state.

The evaluator suggests a sensitivity range of 50 to 200 treatment episodes per year to calculate a range of equipment costs per treatment.

Equipment cost per treatment

As the applicant has not provided an estimation of the 'equipment cost per treatment', a range of possible costs is presented, based on the assumptions detailed below. Scenario 4 indicates assumptions based on information received from a functioning Australian LINAC radiosurgery facility (Smee 2000). Scenario 5 also uses this information, but assumes that costs incurred relate to the conversion of an existing LINAC to radiosurgery capability. Staffing costs are not included in these costing estimates for either gamma knife or LINAC radiosurgery facilities.

Table 33 Assumptions for cost analyses

	Assumptions
Base case	1. Costs come from the application, are unreferenced and therefore may not be accurate. 2. Equipment life of gamma knife and LINAC machine is 14 years. 3. Interest rate of 8 per cent per annum. 4. Cobalt source is replaced after seven years. 5. LINAC is refurbished after six years. 6. LINAC radiosurgery adaptation equipment is replaced after every five years.
Scenario 1	As base case, but: 1. cobalt source for gamma knife is replaced after five years.
Scenario 2	As base case, but: 1. equipment life for gamma knife and LINAC is 12 years; and 2. cobalt source for gamma knife is replaced after five years.
Scenario 3	As base case, but: 1. equipment life for gamma knife and LINAC is 10 years; and 2. cobalt source for gamma knife is replaced after five years.
Scenario 4 **Based on estimates from LINAC radiosurgery facility at Prince of Wales Hospital for a dedicated LINAC unit (Smee 2000).** **Gamma knife costs as per Scenario 1.**	1. Costs for the gamma knife come from the application, are unreferenced and therefore may not be accurate. 2. LINAC purchase and maintenance costs as per Table 31, column 4. 3. Equipment life of gamma knife and LINAC machine is 14 years. 4. Interest rate of 8 per cent per annum. 5. Cobalt source is replaced after every five years. 6. Refurbishment of LINAC is not necessary. 7. Replacement of LINAC radiosurgery equipment is not necessary.
Scenario 5 **Estimated costs for converting an existing LINAC to radiosurgery capability (costs from (Smee 2000).** **Gamma knife costs as per Scenario 1.**	1. Costs for the gamma knife come from the application, are unreferenced and therefore may not be accurate. 2. LINAC purchase and maintenance costs as per Table 31, column 5. 3. Equipment life of gamma knife and LINAC machine is 14 years. 4. Interest rate of 8 per cent per annum. 5. Cobalt source is replaced after every five years. 6. Refurbishment of LINAC is not necessary. 7. Replacement of LINAC radiosurgery equipment is not necessary.

Table 34 indicates the range of cost per treatment episode based on the assumptions in Table 33.

Table 34 Equipment cost per treatment

Number of treatments per year	Equipment cost per treatment (AU$)		Cost ratio – gamma knife costs / LINAC costs
	Gamma knife	LINAC	
Base case			
50	16,751	9,996	1.7
75	11,167	6,664	
100	8,376	4,998	
125	6,700	3,998	
150	5,584	3,332	
200	4,188	2,499	
Scenario 1			
50	18,484	9,996	1.9
75	12,323	6,664	
100	9,242	4,998	
125	7,394	3,998	
150	6,161	3,332	
200	4,621	2,499	
Scenario 2			
50	20,221	10,935	1.9
75	13,481	7,290	
100	10,111	5,468	
125	8,088	4,374	
150	6,740	3,645	
200	5,055	2,734	
Scenario 3			
50	20,581	11,607	1.8
75	13,720	7,738	
100	10,290	5,804	
125	8,232	4,643	
150	6,860	3,869	
200	5,145	2,902	
Scenario 4 (dedicated radiosurgery)			
50	18,484	10,821	1.7
75	12,323	7,213	
100	9,242	5,410	
125	7,394	4,328	
150	6,161	3,607	
200	4,621	2,705	
Scenario 5 (adaptation of existing LINAC)			
50	18,484	6,454	2.9
75	12,323	4,303	
100	9,242	3,227	
125	7,394	2,582	
150	6,161	2,151	
200	4,621	1,614	

Equipment costs per treatment episode for a gamma knife facility ranged from $4,188 (Base Case: 200 treatments per year, equipment life of 14 years, Cobalt sources replaced after seven years) to $20,581 (Scenario 3: 50 treatments per year, equipment life of 10 years and Cobalt sources replaced after five years).

Scenario 4 provides approximates equipment cost estimates for a new dedicated LINAC radiosurgery unit in Australia, and Scenario 5 approximates costs for adapting an existing LINAC facility. Equipment costs per treatment episode for a LINAC facility ranged from $1,614 (Scenario 5: 200 treatments per year, equipment life of 14 years) to $11,607 (Scenario 3: 50 treatments per year, equipment life of 10 years).

As can be seen from Table 34, gamma knife equipment costs per treatment are consistently higher than LINAC equipment costs per treatment under similar circumstances (for example, patient numbers and equipment life). The ratio of gamma knife cost per treatment to LINAC cost per treatment ranges from **1.7 to 2.9**.

Estimates of equipment cost per treatment are dependent on the upfront capital acquisition costs, the useful life of the equipment and the number of treatments per year.

These estimated equipment costs per treatment do not take into account direct medical costs and indirect or societal costs, and do not incorporate staffing costs.

Direct medical costs

Proposed professional fee

The application does not provide a clear indication of the requested Medicare Benefits Schedule fee for gamma knife radiosurgery.

A fee structure of $25,000 based on a $5,000 medical fee and a $20,000 facility fee is presented on page 484 of the submission, and a basic fee of $3,500 is presented on page 470. The submission states that the $3,500 fee will be modified using a formula, however, the applicant did not present a modification formula. It is therefore not possible to determine the applicant's requested Medicare Benefits Schedule fee.

Table 35 indicates current Medicare Benefits Schedule fees for comparator items.

Table 35 Medicare Benefits Schedule fees for gamma knife comparators

Description	MBS Item No.	Fee (AU$)
STEREOTACTIC RADIOSURGERY including all radiation oncology consultations, planning, simulation, dosimetry and treatment	15600	1,309.65
STEREOTACTIC ANATOMICAL LOCALISATION as an independent procedure	40800	491.35
FUNCTIONAL STEREOTACTIC PROCEDURE including computer assisted anatomical localisation, physiological localisation and lesion production in the basal ganglia, brain stem or deep white matter tracts	40801	1,343.05
INTRACRANIAL STEREOTACTIC PROCEDURE BY ANY METHOD not being a service to which item 40800 or 40801 applies	40803	919.80
Arteriovenous malformations		
INTRACRANIAL ARTERIOVENOUS MALFORMATION excision of	39803	2,198.35
Cerebral metastases (NB 10–20 radiation fields is usual)		
CRANIOTOMY for removal of glioma, metastatic carcinoma or any other tumour in cerebrum, cerebellum or brain stem	39709	1,220.65
RADIATION ONCOLOGY TREATMENT using a single photon energy linear accelerator – with or without electron facilities – each attendance at which treatment is given one field	15203	45.90
two or more fields up to a maximum of five additional fields (rotational therapy being three fields)	15204	45.90 + 29.20 for each additional field > 1
RADIATION ONCOLOGY TREATMENT using a dual photon energy linear accelerator with a minimum higher energy of 10MV photons or greater, with electron facilities – each attendance at which treatment is given one field	15207	45.90
two or more fields up to a maximum of five additional fields (rotational therapy being three fields)	15208	45.90 + 29.20 for each additional field > 1
Acoustic neuroma		
CEREBELLO–PONTINE ANGLE TUMOUR removal of by two surgeons operating conjointly, by transmastoid, translabyrinthine or retromastoid approach – transmastoid, translabyrinthine or retromastoid procedure (including aftercare)	41575	1,873.85
CEREBELLO–PONTINE ANGLE TUMOUR removal of, by transmastoid, translabyrinthine or retromastoid approach – intracranial procedure (including aftercare) not being a service to which item 41578 or 41579 applies	41576	2,810.75
CEREBELLO–PONTINE ANGLE TUMOUR removal of, by transmastoid, translabyrinthine or retromastoid approach, (intracranial procedure) – conjoint surgery, principal surgeon	41578	1,873.85
CEREBELLO–PONTINE ANGLE TUMOUR removal of, by transmastoid, translabyrinthine or retromastoid approach, (intracranial procedure) – conjoint surgery, co-surgeon	41579	1,405.35

Source: Commonwealth Department of Health and Aged Care 1999a.

Costs of associated medical and hospital services

In the absence of patient-based costing information for all direct treatment costs, such as associated medical services, diagnostic and investigational services, hospital services, community based health care services, the following table (Table 36) indicates average AN-DRG (diagnosis related group) cost estimates for appropriate currently available procedures. AN-DRG average costs may provide an indication of possible medical costs associated with gamma knife or LINAC radiosurgery treatment and can also provide an estimate of likely costs of comparator interventions, such as surgery. It should be noted that the following AN-DRGs combine a range of primary diagnoses, and as such may not be representative of the true cost of an indication-specific treatment. A patient who receives a craniotomy for treatment of an arteriovenous malformation may not incur the same overall cost as a patient who receives a craniotomy for a cerebral metastasis. The following AN-DRGs represent the possible treatment options for a patient with any of

the three indications examined in this review (arteriovenous malformations, cerebral metastases or acoustic neuroma).

Table 36 AN-DRGs (v3.1) for public and private hospitals, Australia 1996–97

AN-DRG (v3.1) code		Total average cost (public) ($)	Average length of stay (public) (days)	Total average cost (private) ($)	Average length of stay (private) (days)
01-023	craniotomy with complication and/or comorbidity	16,996	16.3	12,962	15.9
01-024	craniotomy without complication and/or comorbidity	10,002	8.8	7,748	9.0
01-033	peripheral and cranial nerve and other nervous system procedures age > 54	4,825	6.4	3,113	6.3
01-034	peripheral and cranial nerve and other nervous system procedures age < 55	2,977	2.4	1,882	1.7
01-059	nervous system neoplasm age > 64	5,109	10.5	5,925	13.7
01-060	nervous system neoplasm age 25 – 64	3,626	7.0	3,855	9.0
01-061	nervous system neoplasm age < 25	2,219	2.3	1,095	2.7

Source: (Commonwealth Department of Health and Aged Care 1999b)

The average cost for intervention ranges from approximately $1,000 to almost $17,000 depending on the type of hospital, age of patients and presence or absence of comorbidities and or complications to the procedure.

Indirect or societal costs

No published Australian data are available for estimating such costs.

Conclusions

As the issues of effectiveness and safety are yet to be conclusively determined, it is not possible to perform a true economic evaluation of the role of gamma knife radiosurgery or comparators in managing patients with arteriovenous malformations, brain metastases and acoustic neuroma.

While a number of 'partial economic analyses' from overseas have been published, the results of these analyses are not directly applicable to the Australian healthcare environment. Differences in unit costs, treatment patterns, resource utilisation and reimbursement systems between Australia and other countries limits our ability to generalise overseas results to Australia.

As the currently available evidence does not allow definitive conclusions regarding the comparative effectiveness and safety of gamma knife to other treatment alternatives, a formal cost-effectiveness analysis cannot be conducted.

Estimates of equipment cost per treatment for gamma knife and LINAC radiosurgery and AN-DRG determined average costs of surgical intervention have been calculated.

Equipment cost per treatment with gamma knife ranged from $4,188 to $20,581 and for LINAC ranged from $1,614 to $11,607 over a range of scenarios. The cost ratio of gamma knife equipment costs per treatment to LINAC equipment costs per treatment ranged from 1.7–2.9 (that is, gamma knife was consistently 1.7 to 2.9 times more expensive than LINAC depending on the costing scenario examined).

Estimates of equipment cost per treatment depend on upfront capital acquisition costs, the useful life of the equipment and the number of treatments per year.

Average direct medical costs are based on AN-DRG estimates and do not differentiate between indications. Average AN-DRG costs may over or underestimate true treatment costs for a specific indication.

Average direct medical costs (as an estimate for gamma knife or LINAC radiosurgery treatment or comparator interventions, such as surgery) ranged from approximately $1,000 to almost $17,000 depending on the type of hospital, age of patients and presence or absence of comorbidities and or complications to the procedure.

A comprehensive Australian-based assessment of clinical effectiveness and costs is needed if more accurate estimates of these parameters and a comparison between treatment alternatives are required.

Conclusions

The poor methodological quality of published data precludes any definitive assessment of the safety and efficacy of gamma knife radiosurgery as a treatment option for arteriovenous malformations, cerebral metastases and acoustic neuroma. Due to differences in the characteristics of patients treated, it is not possible to determine whether radiosurgery treatment is superior to treatment with conventional methods (such as surgery). There is also insufficient information to determine conclusively whether one method of radiosurgery is superior to another.

Safety

There is insufficient evidence to provide a comprehensive assessment of the safety of gamma knife radiosurgery and its comparators. Methodological limitations and patient heterogeneity limits the generalisability of uncontrolled evidence. In no indication was it possible to determine whether one method of radiosurgery was safer than another.

Arteriovenous malformations

Microsurgical excision of arteriovenous malformations results in permanent neurological complication rates of up to 15 per cent. This decreases to less than 5 per cent in patients with small, easily accessible lesions.

Permanent neurological complications occurred in 1–10 per cent of patients treated with radiosurgery.

Cerebral metastases

Little safety information is available from the single, small randomised trial.

Uncontrolled case series suggested that acute radiation-induced oedema developed in up to 20 per cent of patients treated with radiosurgery. Suspected or confirmed radiation necrosis developed as a significant or long-term complication in up to 10 per cent of patients; 6 per cent needed intervention for symptomatic radiation necrosis and in 1 per cent of patients the radiation necrosis was fatal.

Acoustic neuroma

Microsurgical excision results in facial nerve complication rates of up to 20 per cent at one year and useful hearing preservation rates of between approximately 30 per cent and 90 per cent.

Radiosurgical treatment results in facial nerve complications and useful hearing preservation rates similar to microsurgery.

Limited information was available on other procedural complications.

Effectiveness

There is insufficient evidence to provide a comprehensive assessment of the effectiveness of gamma knife radiosurgery and its comparators. Methodological limitations and patient heterogeneity limit the generalisability of uncontrolled evidence. In no indication was it possible to determine whether one method of radiosurgery was superior to another.

Arteriovenous malformations

Patients treated with microsurgery achieve complete excision rates of between 85 per cent and 100 per cent. This increases to between 94 per cent and 100 per cent for patients with small, easily-accessible lesions.

Literature reported obliteration rates for radiosurgery are likely to be an overestimation of the true rate of AVM obliteration due to 1) inadequate patient follow-up and 2) only a proportion of patients eligible for angiography at any given time actually undergoing the procedure.

Two- year obliteration rates (when reported as a percentage of those patients eligible for angiography) range from 26–45 per cent for gamma knife radiosurgery and 44–68 per cent for LINAC.

Cerebral metastases

The single, small randomised trial suggests there may be slightly improved local control for patients treated with radiosurgery plus WBRT compared to WBRT alone. There was, however, no survival benefit for these patients.

The results of uncontrolled case series generally supported those of the randomised trial.

Acoustic neuroma

Microsurgical excision results in complete excision rates of close to 100 per cent (in patients particularly selected for surgery).

Radiosurgical treatment results in tumour control rates (that is, stability or regression of tumour) of between 80 per cent and 100 per cent.

Cost-effectiveness

As the issues of effectiveness and safety are yet to be conclusively determined, it is not possible to perform a true economic evaluation of the role of gamma knife radiosurgery or comparators in the management of patients with arteriovenous malformations, brain metastases and acoustic neuroma.

Cost estimates suggest that the ratio of gamma knife equipment cost per treatment to LINAC equipment cost per treatment is 1.7–2.9 over a range of possible scenarios, i.e. gamma knife was 1.7 to 2.9 times more expensive than LINAC depending on the costing scenario examined.

Overall

Overall, microsurgical resection remains an acceptable therapeutic intervention, particularly for patients with small, easily accessible arteriovenous malformations and acoustic neuromas.

Radiosurgery may be effective treatment for selected groups of patients with arteriovenous malformations and acoustic neuroma, for example those patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention.

Outcomes for patients with cerebral metastases are likely to be influenced more by baseline prognostic factors than by type of treatment.

Evidence does not indicate a difference in outcomes for patients treated with gamma knife or LINAC radiosurgery.

Recommendation

Since there is currently insufficient evidence on comparative safety, effectiveness and cost-effectiveness pertaining to gamma knife radiosurgery, MSAC recommended that additional public funding should not be supported at this time for this procedure.

- The Minister for Health and Aged Care accepted this recommendation on 8 August 2001 -

Appendix A – MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Aged Care 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 Aged Care 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 Aged Care 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:

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care
Associate Professor Richard King	internal medicine
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Associate Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council

Appendix B – Supporting committee

Supporting committee for MSAC application 1028 gamma knife radiosurgery

Dr John Primrose (Chair) MB, BS (Hons), FRACR Senior Medical Adviser Health Access and Financing Divisions Department of Health and Aged Care	medical adviser to MSAC
Associate Professor Michael Barton MBBS, FRANZCR, Cert. Health Economics, Monash Research Director Collaboration for Cancer Outcomes Research and Evaluation, Liverpool Hospital	nominated by the Royal Australian and New Zealand College of Radiologists
Dr Michael Besser MBBS, FRACS, FRCS Canada Chairman Institute of Neurosciences Royal Prince Alfred Hospital	nominated by the Australian Association of Neurologists
Mr Rod Irwin B.Ec. Executive Director Head Injury Council of Australia	nominated by the Consumer's Health Forum
Dr Marianne Vonau MBBS, FRACS Staff Specialist, Neurosurgery Prince of Wales Private Hospital	nominated by the Royal Australasian College of Surgeons
Dr David Webb PhD Medical Physicist Medical Radiation Branch Australian Radiation Protection and Nuclear Safety Agency (ARPANSA)	nominated by ARPANSA

Appendix C – Studies included in the review

Arteriovenous malformations

1 Gamma Knife, LINAC, unspecified
2 selected, consecutive, referred, retrospective, unspecified

Table 37 Gamma knife radiosurgery treatment of arteriovenous malformations

Study	Patients: N, source, history	Type of RS [1]	Study perspective [2]	Hospital	Spetzler–Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Mizoi et al. 1998)	54 53 had embolisation n=31 RS after embolisation, n=1 had RS alone	GK	Consecutive, retrospective Spetzler–Martin grade IV & V only	Tohuku University, School of Medicine	Gr I 0 Gr II 0 Gr III 0 Gr IV 39 Gr V 15	MRI every 6mo for two years; angiog. every 12mo for 2–3yrs n=30 with 2 or 3 year angiography	Complete Obliteration rate Time of Angiog / # Obliterated 12mo 2 24mo 3 36mo 6 Total 11/30 with angiography	Not reported	Worse prognosis than general patients
(Aoki et al. 1996)	236 (137M 99F) mean 31.2yrs (4–71) Presentation: n=175 haemorrhage n=28 seizure n=33 other	GK	June 1990 – Feb 1994 Assume consecutive	University of Tokyo	Not reported	Serial neuro examinations and imaging (CT/MRI) approx every 6months; oblit status eval by angiog.; AVM confirmed by angiog. only	Actuarial rates calculated by Kaplan–Meier (all 236 cases included). Mean time to angiog confirmation 21.4mo 1 yr act complete oblit rate: 36.2% 2 yr act complete oblit rate: 68.9% 3 yr act complete oblit rate: 86.6%	Actuarial risk of post RS imaging changes was 20.0% @ 2yrs (mean 9.4mo (4–19mo). Symptomatic complications of RS developed in 10% of patients @ 2yrs. Permanent complications 4.4%; severe neuro deficits: 2.8%	Overlap with GK group from (Sasaki et al. 1998)
(Flickinger et al. 1996a)	316 patients. 197 with 3yr angiography selected. 118 patients excluded due to incomplete angiographic follow-up.	GK	Aug 1987 – Jan 1992 Selected, 197 of 316 with 3yr angiography; only those with angiography reported	University of Pittsburgh	Not reported	197/316 had angiography at 3 years	Results based on 197/316 with angiographic follow-up at 3 years 142/197 (72%) had complete obliteration. In 12 of these 142, an early draining vein was still present (but coded as complete obliteration, contrary to other publications where coded as incomplete).	Not reported	Selected patients. Results reported based on 197/316 patients with angiography at 3 years no safety info reported; multivariate analysis of obliteration predictors repeated.

Study	Patients: N, source, history	Type of RS [1]	Study perspective [2]	Hospital	Spetzler–Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Flickinger et al. 1998)	332–297 with adequate follow-up MRI (≥ 2yrs) n=187 prior haemorrhage n=143 prior neuro deficit (not incl headache/ seizure) n=220 haemorrhage or neuro deficit.	GK	Retrospective: 1987–94. Patients selected if regular clinical or imaging follow-up for ≥ 2 years after RS	University of Pittsburgh	Not reported	Not reported	Not reported	Post radiosurgery symptomatic sequelae: 30/332 (9.0%); 17/30 resolved 4–27 months post onset; 6/30 present > 24mo. 7/30 still present (but < 24mo follow-up). Actuarial rate of symptom resolution 57.6±11.3 beyond 26mo after onset 7yr actuarial rate for development of persistent symptomatic sequelae = 3.8% PRI changes 90/297 (30.3%)	Neurological Sequelae Multivariate analysis to predict risk of PRI changes and symptomatic sequelae.
(Heffez et al. 1998)	82 (42M, 40F) Mean age 33.3 Presentation: n=44 haemorrhage; n=42 h'ache; n=16 seizures Prior therapy: n=18 surgery n=9 embolisation	GK	Retrospective ?consecutive 'initial 82 patients all treated before Jan 1992' who would have been eligible for 2-year follow-up	Chicago Institute of Neurosurgery & Neuroresearch	Gr I 6 Gr II 25 Gr III 32 Gr IV 12 Gr V 3 Gr VI 4	58/82 with up-to-date angiography @ ≥ 2yrs follow-up; 46/82 with up-to-date angiography @ ≥ 45mo follow-up	At Dec 1993: every pt followed for ≥ 2yrs & 58/82 with up-to-date angiograms (total 31 doc oblit). Oblit rate calc based only on those w/angiog: 37% (21/58) @ 2yrs; 73% @ 3yrs; 84% @ 4yrs (< 50% with angiog) Kaplan–Meier life table analysis 32% (95%CI 22–42) @ 2yrs; 55% (37–73) @ 3yrs; 55% (37–73) @ 4yrs (Mdn 2.8yrs) At Sept 1995: every pt followed for ≥ 45mo & 46/82 with up-to-date angiograms (total 42 doc oblit) Oblit rate calc based only on those w/angiog: 35% @ 2yrs; 67% @ 3yrs; 76% @ 4yrs Kaplan–Meier life table analysis 42% (95%CI 28–56) @ 2yrs; 66% (48–84) @ 3yrs; 79% (61–97) @ 4yrs (Mdn 2.36yrs)	Not reported	Important information re: obliteration rates calculated based on only angiog. confirmed patients, and that pts who have angiog. are often selected on basis of MRI obliteration. Authors attempted to address bias in reporting of obliteration rates.
(Henkes et al. 1998)	64 patients (36M, 28F), mdn age 33 (5-62) Presentation: n=33 haemorrhage; n=21 seizures; n=6 headache; n=4 AVM was incidental finding. All had embolisation before RS	GK	1987–97 retrospective Consecutive patients with embolisation + RS	Unclear embolisation at one hospital, RS at another	Gr I 3 Gr II 13 Gr III 11 Gr IV 17 Gr V 4 Gr VI 16	Not reported	Follow-up included 112 MRI and 32 angiographic examinations after RS. Complete obliterations (by angiog) confirmed in 14 patients (unknown how many had angiography and at what time this was measured).	Only data on safety of embolisation procedure reported, no information on patients who received RS. One death from haemorrhage 18mo after RS.	RS conducted at different hospital. Unknown protocol for angiography/MRI evaluation.

Study	Patients: N, source, history	Type of RS [1]	Study perspective [2]	Hospital	Spetzler–Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Karlsson et al. 1998)	115 (58F, 54M) 3 lost to follow-up: n=89 1x prior GK treatment; n=9 2x prior GK treatments; n=14 fract. RT; n=14 embolisation; n=7 prior surgery: n=112 incl in safety n=101 incl in efficacy	GK	Selection of 115/1,066 treated between 1970–94; previously irradiated	Karolinska Hospital	Not reported	N=101 angiogram	n=9 no change n=11 1–50% volume decrease n=19 51–99% volume decrease n=62 obliteration Unclear at what time point after RS these rates refer to	14 radioinduced complications between 6–57 months (mean 15mo). Haemorrhage: 3 within 2 yrs after RS: annual incidence of 1.8%	Specifically concerned with retreatment after previous RS/RT. Not stated at what time point rates were calculated, what radio-induced complications occurred, the resolution of complications.
(Karlsson et al. 1996)	1604 AVMs	GK	Up until 30 June 1992 Unknown start date 'all 1,604 patients'	Karolinska Hospital	Not reported	1052/1604 with some angiography	Obliteration rates not reported	49/1604 (3%) haemorrhages within 2 yrs of RS treatment. Annual incidence of haemorrhage was 2.1% per year at risk	Study to det. risk factors assoc. with haemorrhage before obliteration, no info on obliteration rates, complications.
(Pendl et al. 1994)	181 patients n=18 Vascular malformations (incl cavernous malformations and angioma) n=13, failed or partial embolisation n=1partial embol + surgery	GK	21/4/92 – 21/4/93 ?assume consecutive n=18 vascular malformations	Karl-Franzens-Universitat Graz, Austria	Not reported	MRI or MR-angiography	Follow-up of 2 to 11 months. In no patient did MRI suggest total obliteration	MR changes observed in n=2 with AVM n=1 reversible neurological deficit n=1 temporary apraxia?	Limited information only
(Pollock et al. 1998a)	315 patients (295 had follow-up of ≥24 mo): 220 with 2yr angiography (203) or resection (7) or new neuro deficit (1) or death (9) selected Presentation: n=135 haemorrhage; n=45 seizures; n=25 headaches; n=15 other symptoms Prior therapy: n=29 surgery; n=40 ≥ 1 embolisation; n=9 clot evacuation; n=5 aneurysm clip	GK	Aug 1987 – Jan 1992 Selected, 220 with either 2yr angiography (203) or resection (7) or new neuro deficit (1) or death (9) selected	University of Pittsburgh	Not reported	203/315 had angiography at 2 years	295 patients had ≥ 2 years follow-up, but only 203 had angiography 134/220 (61%) had complete obliteration ('excellent'=121 'good'=11 or 'fair'=2) 71/220 remained unchanged, 6/220 had a 'poor' outcome; 9/220 died Unclear from way reported how many had angiographically confirmed obliterations and how many were MRI/CT confirmed	All patients who were graded as good, fair or poor developed new neurological deficits Good (oblit + new minor deficit) n=11 Fair (oblit + new major deficit) n=2 Poor (no oblit + any new deficit) n=6 Died n=9	Selected patients uni/multivariate analysis to determine factors associated with successful RS.
(Pollock et al. 1999)	1,033 consecutive patients, Table 1 n=249–227 for AVM. Initial clinical manifestation: n=92 haemorrhage, n=72 seizures, n=90 h'aches Prior therapy: n=15 embolisation	GK	Jan 1990 – Jan 1998 Says consecutive, but discrepancies in patient numbers	Mayo clinic	Not reported	n=97 with f/up angiography ≥ 2yrs after RS	Complete obliteration in 72/97 with angiography at 2 yrs (74%) n=22 had repeat radiosurgery for incomplete obliteration	n=12 developed radiation-induced complications; n=2 had complete resolution; n=10 new permanent neurologic deficits as results of RS; n=13 haemorrhage after RS n=4 fatal haemorrhage n=6 sustained new deficits n=3 recovered completely	Says consecutive patients, but discrepancy in number of AVM patients, Table 1 n=–249 AVM, AVM section says n=227. Less than 50% of patients had angiography

Study	Patients: N, source, history	Type of RS [1]	Study perspective [2]	Hospital	Spetzler–Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Tanaka et al. 1996)	>290 cases 99 with ≥ 12mo angiography selected n=77 haemorrhage Prior therapy: n=24 surgery; n=7 embol; n=2 EBRT; n=17 Surgery to lower CSF pressure	GK	Selected 99/290 on basis of ≥12 mo angiography.	Komaki city hospital	Gr I 2 Gr II 21 Gr III 67 Gr IV 3 Gr V 6	99 patients selected from >290 on whether followed with angiog ≥ 12mo: BUT only n=79 for 1 yr and n=73 for 2 yr oblit rates	Complete Obliteration rates Adults 1yr 27/60 2yr 42/52 Children 14/19 20/21 Total 41/79 62/73 % 52% 85% NB there are also inconsistencies between tables in denominators	n=2 haemorrhages n=1 radiation induced oedema n=1 radionecrosis	99 patients selected from >290 on basis of whether they were followed with angiography ≥ 12 mo, BUT results of obliteration rates indicate only 79 with angiog. 12 mo after RS and 73, 2 yrs after RS
Wara et al 1995	33 (< 21 yrs) (19M, 14F) Mean age 12yrs n=18 with AVMs	GK	Sep 1991-Nov 1993 assume consec < 21yrs n=18 AVMs	UCSF	Not reported	MRI every 6mo with angiogram only when MRI indicated complete obliteration	n=14 with follow-up ≥ 1 month (mean 56.2) n=2 complete obliterations; n=8 partial; n=4 no change	Acute toxicity: oedema with headache or increased neuro symptoms n=2, treated with steroids, resolved	Limited information available on AVMs
(Yamamoto et al. 1995)	121 patients Prior therapy: n=13 surgery; n=13 embolisation; n=4 prior RS (proton or GK)	GK	Jan 1990 – Dec 1993 Assume consecutive	Mayo Clinic	Not reported	n=51 with angiog between 12 and 44 mo. MRI/Clinical exam every 6mo for 2 yrs, then if no nidus on MRI, angiogrpahy performed, if evidence of nidus @ 2yrs, 3yr angiogram ordered.	Angiography between 12 and 44 months, avail only on 51 patients Time after RS # oblit. % 12mo 2/51 4% 24mo 21/51 41% 36mo 35/51 69% >36mo 38/51 75%	Follow-up 12–60 months after RS neurological improvement n=22, stable, n=83; permanent deficit n=6, non-fatal haemorrhage n=4 Fatal haemorrhage n=3 Death, other causes n=3	Same patient group as (Coffey et al. 1995), 8 more patients with angiography

1 Gamma Knife, LINAC, unspecified
2 selected, consecutive, referred, retrospective, unspecified

Table 38 LINAC radiosurgery for treatment of arteriovenous malformations

Study	Patients: N, source, history	Type of RS[1]	Study perspective[2]	Hospital	Spetzler-Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Colombo et al. 1994)	228 (111M, 117F) Mdn f/up 45Mo (1–100) Presentation: n=187 haemorrhage; n=33 seizures, n=7 ↓ neuro function; n=1 exophthalmos Prior therapy: n=35 surg, n=15 embolisation	LINAC	Nov 1984 – April 1992 Appear consecutive Retrospective	City Hospital Vincenza	Not reported	Angiography @ 12, 24, 36mo	Angiography @ 12 mo performed in 156/170 patients with follow-up>1 yr. Complete obliteration rate reported as 47% (ie 74/156 with angiography). Angiography @ 24mo performed in 113/142 patients with follow-up > 2yrs. Complete obliteration rate reported as 80% (ie 90/113 with angiography). RS repeated in 14 patients, surgery in 2 patients and embolisation in 2 patients.	11 patients RS side effects: n=8 sensory motor deficits; n=1 Vth nerve paraesthesia; n=1 hypothalamic syndrome; n=1 confusional syndrome n=6 recovered to normal clinical condition, n=5 unresolved n=17 haemorrhages, n=14 had a prior bleed, n=3 first episode (6days to 2yrs after RS) n=6 fatal cerebral haemorrhage; n=3 required emergency surgery; n=2 static neurological symptoms	
(Duffner et al. 1997)	50, n=16 with AVMs (11M, 5F) n=9 haem; n=5 seizures; n=3 headaches n=5 prior embolisation	LINAC	Retrospective, consecutive Dec 1991 – Jun 1995 'first 50 patients' only 16 AVMs	University of Tubingen	Gr I 0 Gr II 0 Gr III 11 Gr IV 5 Gr V 0	Not reported	'during the follow up 14 patients had complete obliteration'. Not stated how obliteration was defined; what time point it was measured, or how it was measured (eg MR/angiography).	6 patients with 'oedematous changes' (average 8.8mo after RS). n=4 temporary increase in seizures; n=1 deterioration of hemiparesis; n=1 increased ataxia; n=1 permanent hemiparesis; n=1 recurrent heamorrhage	
(Engenhart et al. 1994)	212: first 145 with ≥1 year f'up reported on (71F, 74M) Presentation: n=75 haemorrhage; n=44 seizures; n=19 paresis; n=8 migraine. Prior therapy: n=17 surgery; n=16 embol.; n=4 surg + embol; n=4 aneurysm clip	LINAC	Sep 1983 – Sep 1993 'first 145 cases were investigated for a follow-up of at least 1 year'. Assume consecutive	University of Heidelberg	Gr I 2 Gr II 10 Gr III 30 Gr IV 28 Gr V 20 Gr VI 55	97/120 with angiography at 2 yrs CT/MRI every 6mo; angiog at 2 years or earlier if CT/MRI indicated	Follow-up mean 44.5 mo (1 to 9 yrs) 120 patients with ≥2 years follow up, 97 with angiography 53/97 (55%) with complete obliteration at 2yrs Clinical improvement in neuro symptoms in 65/138 (47.1%)patients; 46/138 remained stable or minimal improvement	n=20 asymptomatic oedema n=16 treatment/oedema associated sequelae (6–24 mo after RS) 10 patients had transient neurological deterioration eg ↑ aphasia/ weakness, hemiparesis, dysphasia: 6 patients worsened permanently n=11 haemorrhage (6mo to 7 years after RS): n=5 fatal; n=3 recovered; n=3 permanent decreased neuro deterioration	Relatively high angiography rate compared to many other studies

Study	Patients: N, source, history	Type of RS[1]	Study perspective[2]	Hospital	Spetzler-Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Friedman and Bova 1992)	80 patients with AVMs (40M, 40F) Presentation: n=41 haemorrhage; n=21 seizure; n=16 headache /incidental; n=2 neuro deficit. Prior therapy: n=18, ≥ 1 surgery; n=≥ 1 embolisation	LINAC	Retrospective, May 1988 – Aug 1991	University of Florida	Gr I 11 Gr II 33 Gr III 30 Gr IV 6	MR every 3–6mo; all patients asked to undergo angiography on a yearly basis regardless of MR results n=41 angiog at 12mo	Mean follow-up 19 mo (3–42), n=48 followed ≥12 mo, 41/48 had angiog at 12mo. Complete occlusion in 16/41 (39%) patients with angiog @ 12mo. n=25 followed for ≥ 24mo, 21/25 had angiog at 24mo. Complete occlusion in 17/21 (81%) patients with angiog @ 24mo.	n=2 seizures ≤ 48 hrs from RS (prev history of seizure) n=2 haemorrhage, annualised haemorrhage rate 1.6%. One patient recovered after prolonged rehab; one remains in rehab. n=4 radiation induced delayed complications including radionecrosis, hydrocepha-lus, headache and oedema (2 permanent, 2 transient)	Earlier report of (Friedman et al. 1995). Kept as provides better obliteration rate information than later publications.
(Friedman et al. 1995)	158 patients (80M, 78 F) 153 clinically evaluable. mean age 39 (13–70) Presentation: n=61 haemorrhage; n=63 seizure; n=30 h'ache/ incidental; n=4 neuro deficit. Prior therapy: n=22 surgery; n=14 ≥ 1 embolisation	LINAC	Retrospective, consecutive May 1988 – Aug 1993	University of Florida	Gr I 11 Gr II 63 Gr III 65 Gr IV 19	n=60/158 angiograms MRI until obliteration suggested, then angiogram. If no oblit at 3 yrs, repeat RS	Mean follow-up was 33 mo (6–70). Angiography at mean 23 mo after RS (12–50 mo) n=48 from 60 (80%) with angiography had complete obliteration	n=7/153 developed seizures within 48hrs of RS (all with past history of seizure). n=6/153 had haemorrhage after RS treatment (1 with past history) (2–11 mo after RS); n=3 fully recovered; n=2 sig permanent deficits; n=1 died n=3 transient delayed RS induced complications: headache, 2x dysphasia n=2 permanent minor neuro deficits (lower extremity weakness; Parinaud's syndrome + hemibody analgesia)	Updated publication of (Friedman and Bova 1992) Only 60/158 (38%) of patients had angiography
(Gobin et al. 1996)	125 patients poor surgical candidates or those who refused surgery Only examines embolisation + RS (conducted as a combined protocol) n=96 had RS after embolisation.	LINAC	1985–1990 ? selected: Only patients treated according to a protocol of embolisation followed by RS	SALT (Ste Anne, Lariboisiere and Tenon Hospitals)	Gr I 0 Gr II 12 Gr III 39 Gr IV 38 Gr V 13 Gr VI 23	n=88/125 had angiograms (n=63 with RS had angiog. Follow-up)	n=14 (12 with angiographic evidence) complete obliteration via embolisation n=96 underwent radiosurgery, of whom 63 had angiographic follow-up at 2 years n=41/63 (65%) with angiography had complete obliteration ≥ 2yrs after RS	n=10 haemorrhages (1 week to 5 yrs after RS) (mean 38.8mo) = postembolisation bleeding rate of 3% per year n=3 fatal haemorrhage; n=5 recovered; n=1 moderate deficit; n=1 severe deficit	paper tends to be report embolisation information, rather than RS
(Kirkeby et al. 1996)	25: 20 with angiography ≥ 2yrs after RT (mean age 39(14–65)) Presentation: n=17 haemorrhage; n=3 seizures Prior therapy: n=10 embolisation	LINAC Fractiona-ted (2 fractions)	'since November 1988' 2 fractions	Rikshospital et, Oslo Norway	Not reported	20/25 had angiog. ≥ 2yrs	14/20 with angiography at ≥ 2yrs had complete obliteration (70%)	n=2 radionecrosis n=2 ≥ 1 bleed after RS n=1 hydrocephalus	Smaller lesions responded better than larger lesions

Study	Patients: N, source, history	Type of RS[1]	Study perspective[2]	Hospital	Spetzler-Martin Grade (n)	Evidence of obliteration	Efficacy outcomes	Safety outcomes	Comments
(Loeffler et al. 1990)	16 children; Mdn age 10.6 (2–20) (3M, 13F) 6 recurrent intracranial tumours 10 AVMs n=9 presented with haemorrhage	LINAC	Apr 1994 – Dec 1988 Assume consecutive	Children's Hospital, Harvard Medical School, Boston	Not reported	8/10 had angiography @ 12 months	Median follow-up 20 months (6–37) 5/8 (63%) with angiography had complete obliterations @ 12 mo	'no serious complications' n=3 evidence of cerebral oedema on CT (one developed headaches and lethargy)	Very small patient numbers only
(McKenzie et al. 1993)	112 patients/ 116 lesions: 86 lesions single dose 59 AVMs ? how many single and fractionated	LINAC	Dec 1986 – Jun 1990 Assume consecutive, data set only contains n=59 AVMs (n=2 received fractionated dosing)	McGill University	Not reported	Not reported	Not reported	Early complications: n=1 headache + right homonymous hemianopsia, resolved within 8 hrs. Delayed complications: n=1 left hemiparesis at 10 months, resolved with steroids, dies of pneumonia at 18mo; n=1 (fractionated dosing) right hemiparesis at 7months, died of bleed at 8mo	Updated publication of (Souhami et al. 1990) n=82 received single dose RS, n=30 received fractionated 'policy was to treat vascular lesions with a single session'
(Miyawaki et al. 1999)	73(35M, 38F); Median age 30yrs (range 5–66). Presenting symptoms: haemorrhage (46); headache (42); seizures (23). History focal neuro sympt (56); neuro deficit at RS (42). Prior therapyembolisation (43); surgery (10); RS (2)	LINAC	Consecutive between 03/88 to 09/91; unknown perspective	UCSF	Gr I 1 Gr II 16 Gr III 36 Gr IV 16 Gr V 3	Initially MRIs every 6mo and angiog. every 12mo; changed to angiog. Only performed when MRI± MRA demonstrated complete/almost complete oblit.	Obliterations measured using 3 methods (see comments column) Method | 3yr Oblit. Rate | 5yr Actuar. rate 1 | 18/28 (64%) | 72% 2 | 28/60 (47%) | 50% 3 | 18/60 (30%) | 33% Obliteration rates decreased with increasing AVM size	Acute complications: n=12 suffered acute transitory symptoms: seizures (4); naus/vom (7); new/worse headache (5); fever (1) Delayed complications: 13/73 (18%) reqd medical or surgical intervention for treatment related complications (5yr act rate of 21% (95%CI 13–32%) 5yr act rate of radiation necrosis req surg resection 7% (95%CI 2–18%) n=10 serious permanent complications; n=12 had 14 haemorrhage; n=5 fatal haemorrhage (5/7 non-fatal had significant long-term morbidity). Kaplan–Meier: 5 year actuarial rate of haemorrhage 12%(95%CI 6–23)–16% (95%CI 8–31); 7 year actuarial rate 33% (95%CI 18–54)–55% (95%CI 30–83)	Obliteration rates calc by 3 methods 1) only angiographic data; 2) either angiog or MRI to define obliteration and failures; 3) only angiographic data for obliteration and angiog or MRI failure, retreatment (Sx or RS) or death from haem = failure. Authors attempted to address bias resulting from angiographic obliteration rates by reporting obliteration rates in 3 ways.

(Pelissou-Guyotat et al. 1997)	90: multimodal-ity tx including 1 or more of surgery, embol-isation and RS. Surgery alone: n=19, 21% Embol + surg: n=19, 21% Embol alone: n=18, 20% RS alone: n=15, 17% RS + embol: n=15, 17% RS + surgery: n=4, 4%	LINAC	1990–95 Assume consecutive More recent data set, includes patients previously reported on	Hopital Neurologique et Neurochirurgica l, Lyon	Gr I 4 Gr II 25 Gr III 32 Gr IV 25 Gr V 4	74/90 patients with angio-graphic follow-up at 2 yrs	Eradication rates for 74 with angiographic follow-up. Surgery alone: 82% Embol + surg: 100% Embol alone: 6% RS alone: 87% RS + embol: 76% RS + surgery: 100%	Complications Overall gp / RS gp No deficit: 64 (71%) / 31 (91%) minor deficit: 16 (18%) / 2 (6%) deficit: 6 (7%) / 1 (3%) vegetative: 4 (4%) / 0 or dead	Updated data set of (Deruty et al. 1996). Unclear how many patients in each treatment group actually had angiographic follow-up, also unclear what complications were
(Pica et al. 1996)	41 patients (19F, 22M) Mdn age 33.5 (9–61) Presentation: 61% haemorrhage; 20% seizure; 5% ↓ neuro stat; 15% intract headache. Prior Therapy: n =6 surg, n=16 embolisation, n=1 surg + embolisation, n=18 RS alone	LINAC	Dec 1989 – Dec 1992 Assume consecutive	Centre Hospitalier Lyon Sud	Gr I 1 Gr II 6 Gr III 18 Gr IV 14 Gr V 0 Gr VI 2	CT/MRI every 6mo; angiog only if MRI indicated obliteration	Mdn follow-up 34 mo (3–55) 29/41 angiog @ 1yr: total oblit in 4/29 (14%) 32/41 angiog @ 2yr: total oblit 26/32 (81%) >80% oblit 3/32; <80% oblit 3/32 Complete oblit rate correlated with lower Spetzler–Martin Grade	2 haemorrhage, 1 fatal, 7mo from RS Neuro outcomes : Glasgow Outcome Scale (GOS); n=11 (27%) RS assoc toxicity 8–24 mo after RS: n=4 (GOS1) temp neuro deterio-ration with complete recovery; n=3 (GOS2) ↑ seiz freq w/ anticonvulsant and steriod therapy; n=4 (GOS 4) serious and irreversible neuro dysfunction, from radiation necrosis & oedema	Association between total obliteration and AVM dimension and mean volume. Surgery (n=1) & embolisation (n=1) after unsuccessful RS
(Schlienger et al. 2000)	201–169 evaluable Mdn age 33 (6–68) Prior therapy: 6% Surg, 36% embol, 3% Surg + embolisation, n=55% RS alone	LINAC	169 evaluable patients from 201 treated 1990–93. Not evaluable = prior RS (4), lost to follow-up (foreign 20); angio refused (2); unrelated death (2); incomplete dosimetric data (4)	Centre Hospitalier Sainte-Anne, Hopital Tenon	Not reported	Assume all pts had angiography (48–96 mo follow-up)(exclusion criteria was refusal to undergo angiog)	108/169 had complete obliteration (48–96 mo after RS)	4/169 (2.3%) recurrent haemorrhage; 4/169 new seizures 2/169 new transient neuro deficits; 1/169 new permanent neuro deficit	Multivariate analysis indicated no prior embolisation and monoisocentric radiation dosing were independent predictors of successful obliteration
(Sebag-Montefiore et al. 1995)	101 patients with inoperable AVMs Mdn age (9–66) Patient history: n=80 ≥1 haemorrhage; n=27 epiliepsy; n=33 neuro deficit. Prior therapy: n=14 ≥ 1 embolisation (3 pts with perm-anent neuro deficit as a result); n=14 ≥ 1 surgical procedure	LINAC	March 1989 – Dec 1993 Assume consecutive	St Bart's Hospital, London	Not reported	52/101 with follow-up angiography (11–42mo after RS)	Complete Obliteration rate <12mo: 1/3 12-17mo: 7/8 18-24mo: 14/23 25-30mo: 9/12 31-36mo: 3/4 37-42mo: 0/2	2 year actuarial bleed risk 5.1% n=2 early re-bleed (4 and 7 mo) n=2 late re-bleed (18 and 20mo) n=7 neurological complications as a results of RS (n=2 reversible) (mdn latency 17 mo) actuarial risk of neurological complications was 7.7% @ 2 yrs (n=58 at risk); 3 year act complic rate 9.9% (n=34 at risk)	Same patients (Falkson et al. 1997) and (Sims et al. 1999). Only –50% of patients with angiography

(Smith et al. 1997)	54, 37 selected with angio-grams: n=11 RS alone, n=5 RS + embol, n=7 RS + surg, n=31 RS + surg + emb	LINAC	Retrospective 37 with angiography selected of 54 between 1990 and 1995	Barrow Neurological Institute	Gr I 0 Gr II 0 Gr III 17 Gr IV 19 Gr V 12	Angiography on 37/54 patients (5–66mo after RS)	13/37 (35%) with angiography had complete oblit (3/11 Gr 5; 7/12 Gr 4; 3/14 Gr 3) RS alone 1/6 oblit; embol + RS 3/5 oblit RS + microsurg + embol 10/23	n=5 haemorrhage following RS n=1 fatal haemorrhage, n=1 permanent morbidity n=1 radiation necrosis with permanent neuro disability	Selected patients on basis of angiog 'RS not really an alternative to microsurgery, … valuable treatment option for pts with AVM in locations with excessive/ unaccept-able surgical risk'
(Souhami et al. 1990)	n=33 with inoperable AVMs n=2 had two fractions of RS (15M, 18F) Mdn age 26 (9–69) Presentation n=19, haemorrhage; n=7 seizures; n=3 headaches; n=4 other neuro symptoms. Prior therapy: n=5 surgery; n=1 embolisation (x3)	LINAC	Assume consecutive Dec 1986 – Dec 1988	McGill University	Not reported	n=21 with angiog at 12mo	Mdn follow-up 16 months (7–32): 8/21 with angiography ≥ 12mo (Mean 17 mo) from RS had complete obliterations (38%)	n=3 late complications of RS n=1 haemorrhage n=2 hemiparesis as a result of oedema	Partial data set of (McKenzie et al. 1993)
(Touboul et al. 1998)	100(54M, 46F) Mdn age 30.7 (7–70)yrs. Presenting symptoms: n=67 haemorrhage, n=34 neuro deficit; n=30 seizure; n=2 migraine. Prior therapy: n=13 surgery); n=28 ≥1 incomplete embolisation; n=3 surgery + embolisation	LINAC	Consecutive May 1986 – December 1989	SALT (Ste Anne, Lariboisiere and Tenon Hospitals)	Gr I – III 79 Gr IV 3 Gr V 0 GrVI 18	Angiography in all patients Mdn angiog follow-up 37.5mo (7–117mo)	Absolute obliteration rate was 51%(mean angiographic follow-up of 42±2.3mo, mdn 37.5mo, range 7–117mo); 3year actuarial rate: 40±5% (n=45); 5 year actuarial rate was 62.5±7% (n=15)	Delayed complications in 8 patients: persistent headache (1), increased seizures (2); mental deterioration (1); paresis (2); permanent symptomatic post radiosurgery imaging changes (1); localised symptomatic radionecrosis (1). Mean interval from treatment to complication was 39±11mo. 3 and 5 year actuarial rates of delayed complications 4±2% (n=94) and 7.4±3% (n=70) respectively. Recurrent haemorrhage from residual AVM occurred in 10 patients (mean interval from treatment to haemorrhage was 39±9.6mo, mdn 37mo, range 2–114mo).	Also reported univariate and multivariate analysis of influencing factors, and sub group analysis of obliteration rates. Angiography in all patients.
(Young et al. 1997)	50 (30M, 20F) mean 37.5 yrs (16–68). Presentation: n=26 haemorrhage; n=18 seizures; n=4 headache; n=2 incidental. Prior therapy: n=3 surgery; n=17 embol.; n=6 embol. + surg; n=24 RS alone	LINAC	July 1989 – Feb 1996 Consecutive, retrospective, 'first 50 patients eligible for a minimum of 3 years follow-up	University of Toronto	Not reported	n=39 had angiography at 2 or 3 years (median 2yrs 4mo)	Results reported on n=50 eligible for 3-year follow-up, 45 evaluable at 3 years 25/50 (50%) have angiographically confirmed complete obliteration at 3yrs	n=2 haemorrhage (1 with remaining mild hemiparesis, 1 fatal) n=1 acute dysphasia 6hrs post-RS n=1 worsening short-term memory	Authors acknowledge bias in reporting angiographic obliterations; reporting bias has been minimised by authors as obliteration rates reported as % of those patients eligible for 3-year follow-up, not of those with angiography.

Cerebral metastases

1 Gamma Knife, LINAC, fractionated LINAC
2 I = initial; R = recurrence
3 n = patients/metastases
4 months unless otherwise specified
5 from statistical anlaysis of outcomes, multimariate and univariate

Table 39 Case series publications of radiosurgery treatment of brain metastases

Study	Type of SRS[1]	Treatment plan[2]	Patient characteristics[3]	Crude local control	Actuarial control	Median survival[4]	Actuarial survival	Adverse effects	Factors associated with improved local control/survival[5]
1. (Weltman et al. 2000)	LINAC	SRS + WBRT (n=58) SRS	n=65/125 1–5 metastases ≤ 30cm3 KPS ≥50 Excluded if fast progressing systemic disease/surgical intervention necessary	Not reported	Not reported	6.8 months from RS	Not reported	Not reported	Survival *Cox Model:* Age, KPS (≤70 vs ≥80), systemic disease status, largest lesion volume (cm^3), number of lesions (borderline). *Stepwise selection:* KPS (≤70 vs ≥80), systemic disease status
2. (Muacevic et al. 1999) retrospective case series	GK	Surgery + WBRT (I) SRS (I)	Surg + WBRT n=52/52 SRS n=56/56 single lesion only ≤3.5cm diameter stable systemic disease	Surg + WBRT SRS: 94.7%	1 yr freedom from local recurrence. Surg + WBRT 75%: SRS 83% (p=0.49): 1yr freedom from distant recurrence. Surg + WBRT 90%: SRS 68% (p=0.0025)	Surg + WBRT 68weeks SRS 35weeks	Surg + WBRT (1yr) 53% SRS (1yr) 43% (p=0.19)	Transient perioperative morbidity Surgery 7.6%; RS 8.9% Mortality Surgery 1.9%; RS 1.8% 7.1% Radiogenic complic. (≤6mo)	Survival Patients with metastasis from breast cancer survived longest (mdn 80 weeks) cf bronchial carcinoma Mdn 24 weeks; KPS>70; Treatment variable (SRS vs Surgery) not significant. *1 yr neurological death rate:* Surg + WBRT 37%, SRS 39% (p=0.8). *1yr systemic death rate*: Surg + WBRT 37%, SRS 51% (p=0.3).
3. (Schoeggl et al. 1999) retrospective case series	GK	SRS (Unclear whether WBRT also given)	n=97/266 multiple (2–4) metastases 45% with systemic metastatic disease	91% tumours 94% patients Median time to local progression 7 months	Not reported	6.1 months from SRS	26 % (1 year)	5% Transient nausea/vomiting/ dizziness, RS related complic: oedema 5%; tumour necrosis 1%	Survival *Univariate:* KPS > 70, no systemic metastases. *Multivariate* KPS > 70; no systemic metastases.
4. (Sneed et al. 1999) retrospective comparative case series	GK	SRS + WBRT (I) SRS (I)	n=43/? n=62/? Newly diagnosed brain mets	Local crude FFP SRS + WBRT 84% SRS 79%	Actuarial FFP SRS + WBRT 94% (6month); 79% (1 yr) SRS 94% (6month); 71% (1 yr) (p=0.3) Actuarial brain FFP – (incl local failures + new brain lesions) SRS + WBRT 89% (6month); 69% (1 yr) SRS 66% (6month); 28% (1 yr) (p=0.008)	Measured from date of diagnosis of brain metastases SRS + WBRT 11.1 months SRS 11.3 months	SRS + WBRT 46% (1 year) 27% (18 months) SRS 48%(1 year) 31% (18 months)	Transient (self limiting ≤ 2 weeks: 6% Late complications (4mo–1.7yrs) 6% symptomatic necrosis requiring intervention 1% fatal radionecrosis	Survival (univariate stratified by treatment) no extracranial metastases; higher KPS; smaller total target volume. Brain FFP (including local failures + new brain lesions): the effect of treatment arm remained significant at p=0.03 with a hazard ratio of 0.476 after adjustment for worse pattern of enhancement, number of lesions treated and interval from 1° diagnosis to brain metasteses diagnosis in a multivariate model.

Study	Type of SRS[1]	Treatment plan[2]	Patient characteristics[3]	Crude local control	Actuarial control	Median survival[4]	Actuarial survival	Adverse effects	Factors associated with improved local control/survival[5]
5. (Lavine et al. 1999) retrospective and prospective case series	GK	SRS + WBRT (n=2) SRS	n=45/93 metastatic melanoma newly diagnosed brain mets	32/45 with imaging 97%	Not reported	8 months from RS	Not reported	Transient (≤72hrs duration): 9% seizures; 7% nausea/vomiting;7 % increase paresis; 2% increase confusion	Not reported
6. (Pirzkall et al. 1998) retrospective case series	LINAC	SRS + WBRT (I) SRS (I)	SRS + WBRT n=78/107 SRS n=158/204 1–3 lesions no previous WBRT KPS ≥50%	Not reported	SRS + WBRT 92% (1 year) 86% (2 years) SRS 89% (1 year) 72% (2 years)	Actuarial median from RS 5.5mo (range 0.4–91mo)	SRS + WBRT 30.4% (1 year) 13.9% (2 years) SRS 19.2% (1 year) 8.3% (2 years) (p=0.75)	Transient (2–4mo after RS): 18% perifocal oedema; 1% suspected radionecr.; 0.5% confirmed radionecr.	Survival lesion diameter < 17mm, no extracranial disease, KPS > 80%, age < 50yrs
7. (Schoggl et al. 1998)	GK	SRS + WBRT SRS	SRS + WBRT n=9/19 SRS n=14/26 renal cell carcinoma only 1–4 lesions	96%	Not reported	Overall series 11 months (from RS)	1 year actual survival 48%	9% perifocal oedema 4% radionecrosis	Not reported
8. (Mori et al. 1998a) retrospective case series	GK	SRS + WBRT SRS	n=35/52 (71% single) renal cell carcinoma KPS ≥ 50% ≤3.5cm diameter 74% with active systemic dis.	90% tumours 88% patients	Not reported	Overall series From RS 11mo From diagnosis 14mo	Overall series Actuarial survival from RS 43% (1 year) 22% (2 year)	6% suspect randionecrosis 3% radiation injury	Survival *Univariate*: age < 55yrs; KPS ≥ 90; nephrectomy prior to RS. *Multivariate*: age < 55yrs; no active systemic disease; chemo/immunotherapy after RS
9. (Cho et al. 1998) retrospective case series	LINAC	SRS + WBRT (I) SRS (R (40) + I(2))	SRS+WBRT n=31 (n=6 prior surg) SRS n=42 (n=20 prior surgery)	Not reported	Actuarial local progression free survival 80% (1 year) 80% (2 years) Regional progression free survival 58% (1 year) 44% (2 years)	7.8 months from RS	32% (1 year) 21% (2 years)	18% radiation induced swelling (≤72hrs after RS); 3% radionecrosis (6–12mo after RS)	Survival KPS > 70; absence of extracranial disease; single metastases (vs multiple)
10. (Grob et al. 1998) retrospective case series	GK	SRS (R + I)	n=35/70 metastatic melanoma 1–3 metastases < 3cm diameter no other immediately life threatening metastases KPS > 60	56 lesions eval (3 months, others died) 55/56 controlled 98.6% if include 8 lesions which may have progressed 55/64 (86%)	Not reported	7 months from RS	Not reported	6% increase in seizures 6% radiation necrosis	Not reported
11. (Mori et al. 1998b) ? Prospective case series	GK	SRS + WBRT (I) SRS (I + R)	n=60/118 metastatic melanoma KPS >50% <3.5 cm diameter 60% active systemic mets	46 pts/72 tumours evaluable (imaging) 90% (tumours) 85% (patients)	Not reported	7 months from RS	21% (1 year) 11% (2 years)	Not reported	Survival *Univariate*: No systemic disease; chemo/ immunotherapy (after RS) *Multivariate*: no systemic disease; single vs multiple lesions

Study	Type of SRS[1]	Treatment plan[2]	Patient characteristics[3]	Crude local control	Actuarial control	Median survival[4]	Actuarial survival	Adverse effects	Factors associated with improved local control/survival[5]
12. (Tokuuye et al. 1998) – small cerebral lesions, metastatic reported only	Fractio n-ated LINAC	Fractionated SRT	n=64/95 ≤ 5cm diameter 1–3 metastases	Not reported	91% (1 year)	8.3 months from RS	33% (1 year)	4% chronic complications associated with radiosurgery 7.7% 1 year actuarial of complications	Survival No active extracranial tumours Performance status Primary site (lung carcinoma vs others)
13. (Williams et al. 1998) retrospective case series (lung vs non-lung)	LINAC	Lung n =14 (18 mets) SRS + WBRT n=13 SRS alone n=1 Non-lung n=16 (27 mets) SRS + WBRT n=14 SRS alone n=2	n=30/45 KPS ≥70% Controlled/absent primary dis ≤ 3.5cm diameter patients split lung vs non-lung	Lung 100% tumours Non-lung 52%	Not reported	Lung 7.9 months from RS Non-lung 8.4 months from RS	Not reported	Not reported	Not reported
14. (Seung et al. 1998) retrospective case series	GK	SRS + WBRT (I) SRS (R + I)	n=55/140 (113 with imaging) metastatic melanoma ≤ 3cm diameter KPS ≥ 70 Single or multiple metastases 90% had systemic metastases	Not reported	Actuarial FFP 89% (6month) 76% (1 year) Actuarial FFP – intracranial (incl local failures + new brain lesions) 41% (6 months) 24% (1 year)	35 weeks from RS	58% (6 months) 34% (1 year)	7% acute RTOG grade ≥2 morbidity 9% late RTOG grade ≥2 morbidity	Survival *Univariate*: KPS; Max lesion diameter; Total target volume (contin + categorical variable) *Multivariate*: Total target volume (contin var)
15. (Kim et al. 1997) retrospective case series	GK	SRS + WBRT (I + R) SRS (I + R) n=16 underwent surgery prior to RS	n=71 n=7 1–4 metastases NSCLC carcinoma ≤3cm diameter 31.2% with active systemic dis	85% tumours 88% patients Median time to local progression 30 months	Not reported	Overall series From RS 10 mo From diagnosis 15 mo	Not reported	16% peritumoural oedmea 3% delayed intratumoural haemorrhage 1% tumour necrosis	Survival *Univariate*: No neuro deficit at RS; no active systemic disease *Multivariate*: no active systemic disease; metastases < 2cm; no intratumoral necrosis; chest lesion resection prior to RS
16. (Gieger et al. 1997) retrospective case series	LINAC	SRS + WBRT (I) SRS (I + R)	n=12/21 metastatic melanoma	57%	Not reported	8 months from RS	66% (6 months) 36% (1 year)	Not reported	Not reported

Study	Type of SRS[1]	Treatment plan[2]	Patient characteristics[3]	Crude local control	Actuarial control	Median survival[4]	Actuarial survival	Adverse effects	Factors associated with improved local control/survival[5]
17. (Fernandez-Vicioso et al. 1997) – retrospective case series	LINAC	SRS + WBRT (R + I) SRS (R + I) (n=10)	n=48/48 single metastases only KPS ≥ 70 < 4cm diameter lesion ≥ 1cm from optic chiasm reasonably well controlled primary tumour	81% patients	Actuarial local control 73% (1 year) 73% (2 years)	8 months from RS	37% (1 year) 17% (2 years)	15% acute transient toxicity 8% long-term toxicity 2% fatal haemorrhage in metastasis	Survival *Univariate and Multivariate* age (≤ 65 vs > 65); Initial KPS (≤ 70 vs ≥ 80) *Local control*: recurrent vs newly diagnosed lesion

Acoustic neuroma

1 Gamma Knife, LINAC, unspecified
2 selected, consecutive, referred, retrospective, unspecified

Table 40 Gamma knife treatment of acoustic neuroma

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up: type and % patients	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Miller et al. 1999)	n=82 (follow-up 80/82: Mdn 2.3 yrs (0.1–6yrs)) n=42 stand. dose protocol n=40 reduced dose protocol	GK	Prospective Consecutive 01/90–15/12/95 2 groups: Standard dose 1990–1993 (follow-up ↑ 6yrs) reduced dose 1993–1995 (follow-up 0.1–2.5yrs)	Mayo clinic	78/82 with follow up imaging 13/79 (16%) had useful hearing prior to treatment	Trigem neurop 'signif' = pain + functional impariment 'mild'=limited loss of sensation Facial nerve function: House–Brackmann (HB) Hearing: Gardner–Roberston (GR) ? definition of lesion/ or symptom regression/ resolution	Tumour control 78/82 w/ imaging 75/78 (96%) stable or partial regression 3/78 (4%): radiographic progression 2/78 (3%) progession req. surgery n=1 died of cvs event unrelated to SRS at 4mo	Trigem neuropath: 17/82 with new/progressive trigem neurop 11= mild; 6=significant (Mdn onset 6mo (1wk – 1.5yrs)); 4 complete recovery (1–13mo) 5 partial improvement (6–45mo) 1yr Actuarial Incidence = 20% (95%Ci, 11–29%) 2yr Actuarial Incidence= 24% (95%CI, 14–34%) Facial neuropath: 19/82 with new/ progressive facial neuropath (Mdn onset 0.5yr (0.3–1.3yrs)); 2 complete recovery (5–7mo) 6 partial subjective improvement (3–39mo) 1yr Actuarial Incidence = 21% (95%Ci, 12–30%) 2yr Actuarial Incidence = 26% (95%CI, 16–36%) Hearing preservation:13/79 had useful hearing (GR I–II) prior to SRS Overall actuarial incidence of useful hearing preservation: 1 yr 92% (95%Ci, 78–100%) 2 yrs 39% (95%CI, 12–65%) Other Complications: n=6 persist, intermitt hemifacial spasm (2 resolved) n=1 hyperglycemia from oral CS n=1 hydrocephalus from edema/necrosis w shunt req'd	Eligibility criteria clearly defined; safety results also split by dose regimen used
(Walch et al. 1999)	n=79 mean age 52 (10–81) n=51 initial; n=28 remnant or recurrent n=7 NF–2 diam. 5.3–37.7mm	GK	Retrospective review 1992–1995 failed or refused surgery; residual/recurrent tumour; only hearing ear; bilateral; age; poor surgical risk	University of Graz, Austria	69 avail for audiometric evaluation 21/69 (30%) had useful hearing prior to treatment 23/69 (33%) were deaf	Facial nerve function: House–Brackmann (HB) Hearing: Gardner–Roberston (GR)	No tumour growth after follow-up 3–6yrs 10% regression 90% stable	Facial neuropathy (HB) 1/79 improved; 72/79 stable; 6/79 deterioration Trigeminal neuropathy 10 patients with symptoms prior to SRS; 1 improved; 2 new cases Hearing 9/69 evaluable patients had a deterioration in hearing; additional 7/69 lost all hearing; 1/69 improved 21/69 with useful hearing: 14 maintained useful hearing after treatment	

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up: type and % patients	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Vermeulen et al. 1998)	n=52 (54 tumours) Mean age 58 Intracanalicular n=14/14 tumours Mean diam 0.8cm Extracanalicular n=38/40 tumours Mean diam 1.8cm	GK	Sept 1993 – April 1997 assume consecutive results split by intra/extracanalicular	Northwest hospital	Mean follow-up1.6 yrs(0.1–3.3) Imagaing avial for 12/14 (8 with 1yr imaging) and 30/38 respect (17 with 1yr imaging)	Local control: no growth or regression on subsequent MRI scan at 6mo intervals Acute symptoms within 12mo of SRS Chronic after 1 yr. Facial nerve function: House–Brackmann (HB)	Intracan tumours: 12/12 decrease or no change 8/8 at 1 yr Extracan tumours: 26/30 decrease or no change 14/17 at 1 yr	Facial neuropathy acute and new Intracanalicular tumours: 6/14 (45%) Extracanalicular tumours 5/40 (13%) Trigeminal neuropathy: acute and new Intracanalicular tumours 3/14 (21%) Extracanalicular tumours 1/40 (3%) Vestibular disturbances new and acute Intracanalicular tumours 4/14 (29%) Extracanalicular tumours 0/40 (0%) Subjective decrease in hearing Intracanalicular tumours 2/14 (14%) Extracanalicular tumours 9/40 (23%)	
(Thomassin et al. 1998)	n=138/138 tumours No NF-2	GK	July 1992 – May 1994	Chu Timone, Marseille	104 with 3yr test/retest audiology 48/138 (35%) with useful pre-treatment hearing 19/138 patients deaf at treatment 85 assessable	Hearing: Gardner–Roberston (GR) and evaluated by tonal and vocal audiometry	Not reported	Hearing only in 85 assessable patients (GR grade I–IV) At three year assessment 47 remained in GR I–IV; 57% with some preserved hearing 43% deteriorated; 4% improved, 10% went completely deaf 48 patients with useful hearing (GR I-II): (19/48) 40% preserved some hearing (50% (10/19) of these preserved useful hearing)	Specifically hearing outcomes
(Kwon et al. 1998)	n=88/? tumours mean age 43.7 (13–72); n=9 NF-2 n=51 initial treatment	GK	Retrospective review May 1990 – for six years Mean follow-up 52mo (7–84)	University of Ulsan, Seoul, Korea	N=63/88 with MRI 3/38 with some hearing prior to treatment	Not reported	27/63 stable 33/63 regression 3/63 progression Total tumour control rate 95%	n=1 Immediate post-op severe vomiting n=3 post-op shunt insertion after GK n=2 surgical removal of tumour after GK Facial neuropathy n=7 (8%) Trigeminal neuropathy n=3 (3%) Hearing: 3 pts with hearing prior to GK; 2/3 preserved (11–19mo)	Risk factors for facial palsy analysed: tumour volume, number of isocentres, marginal dose and marginal isodose all non-significant
(Kondziolka et al. 1998)	n=162 (71M, 91F) Mdn age 60 (28–83) NF-2 patients excluded n=42 (26%) previous Sx n=1 previous fractionated RT	GK	Consecutive patients between 1987 and 1992 NF-2 patients excluded Follow-up: serial imaging every 6mo for 2yrs, 1/yr for 2 yrs, then 1/ 2yrs; survey questionnaire sent 5–10 after SRS	Uni of Pittsburgh	5–10 years after SRS Evaluable patients Facial Nerve n=155 Trigem nerve n=162 Hearing n=85 76/162 deaf 32/165 with useful hearing prior to treatment	Facial nerve function: House–Brackmann (HB) Hearing: Gardner–Roberston (GR)	1yr: 74% stable; 25% regression; 1% progression 2yrs: 48% stable; 47% regression; 5% progression 3yrs:38% stable; 59% regression; 3% progression NB: unclear patient numbers at each time point	All neurological deficit developed ≤ 28mo from RS; no new deficits from 3–10 yrs *Facial Nerve*:122/155 (79%) preserved normal function; 122/144 (85%) in those with prior normal function *Trigeminal nerve*: 119/162 (73%) preserved normal function; 119/142 (84%) in those with prior normal function *Hearing (GR):* no change in GR in 43/85 (51%); 32 pts with useful hearing prior to RS; 15/32 (47%) preserved useful hearing; some hearing preserved in 52/85 (61%); 4% new/worse ataxia; 2% hydrocephalus requiring shunt insertion	Long-term outcomes measured NB Methods reports 162 patients, cf figure 2, n=281 @ 1–2yrs, 171 @3–4 yrs etc. Patient numbers do not match in different areas of report 4 patients had tumour resection by 3 yrs

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up: type and % patients	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Ito et al. 1997)	n=46 (21M, 25F) Mdn Age 54 (13–77) Unliateral only F/up Mdn 39mo (4–73) ? unclear previous Tx	GK	Retrospect Assume consecutive June 1990 – June 1994	University of Tokyo	Not reported 38/46 with some hearing prior to treatment	Hearing neuro-otological examination: pure tone audiometry PTA=pure tone average, LTA = low tone average HTA = high tone average Facial nerve function: House–Brackmann (HB) vestibular nerve function meas by caloric response	Tumour control 10/46 (22%) regression ≥ 2mm; 34/46 (74%) unchanged; 2/46 (4%) progression ≥ 2mm	Total hearing loss 7/38 (18%) with any measurable hearing became totally deaf after SRS (Mdn onset 3mo) PTA Elevation ≥20dB 23/38 (61%) with any meas pre-tx PTA (Mdn onset 8mo) Loss of vestibular nerve function 9/13 (69%) with pre-tx preserved caloric response (Mdn onset 8mo) Any facial palsy (delayed/exacerbation) 10/46 (22%) (Mdn onset 6mo) Any facial nerve dysfunction (incl palsy/transient spasm): 23/46 (50%) (Mdn onset 6mo) Any trigeminal nerve dysfunction (incl delayed): 14/46 (30%) (mdn onset 5.5mo)	Risk factor analysis for each neuro-otological complication calculated also for each event. Audiometry measure for high tone average and low tone average also (not reported here as other papers only report PTA)
(Flickinger et al. 1996b)	n=273 Unilateral only CT guided SRS: 08/87–09/91 n=118 (mdn f/up 47mo) MR guided SRS 09/91–12/94 n=155 (mdn f/up 13mo), NB MR gp smaller tumours than CT gp. No info re previous tx	GK	Assume retrospect Assume consecutive Aug 1987 – Dec 1994 Mdn follow-up 24mo (3–9)?? 2 groups: CT guided SRS (Aug 1987 – Sept 1991) MR guided SRS (Sept 1991 – Dec 1994)	University of Pittsburgh	211 f/up > 12 mo 63/273 with useful hearing prior to treatment; 127/273 were deaf at treatment	Clinical tumour control: absence of sig/sust. Tumour growth not requiring defin Tx (ie no Sx) Radiol tumour control (no growth by CT/MR) absence of any documented change in tumour volume Facial nerve function: House Brackmann (HB) Hearing: Gardner Roberston (GR)	Tumour control: Entire series: 7yr act clinical control rate: 96.4%±2.3% 7yr act radiol control rate: 91.0%±3.4% 7yr act rate for progression not req surgery: 5.4% (crude rate 2.2%, n=6) Tumour response: shrinkage in 81/211 w. f/up≥12 mo,	Facial neurop: (↑ HB grade) Developed in 36/260 eval pts Act incidence 17.2% ±2.7% @3yr (&7yr) Trigem neurop: (temp/perm subject change) Developed in 49/273 eval pts : Act incidence 22.6% ±2.9% @3yr (&7yr) Hearing (↑ GR grade)Developed in 53/146 pts w. GR I–IV preop hearing: Act incidence 45.4% ±4.9% @3yr (&7yr) loss of testable speech discrimination deterioration to GR class V: 38/146 pts: 31.6%±4.4% Act rate at 3 (&7)yrs Loss of serviceable hearing (deterioration from GR class I–II, to III–V) 25/63 w/ class I–II preop hearing deteriorated Act rate 48.2%±8.5% @3yr(&7yr) ie 38/63 maintained useful hearing	Results also split by whether CT or MRI treatment planning
(Forster et al. 1996)	n=27/29 tumours (14M, 13F) n=26 NF–2	GK	1986–89 failed or refused surgery; residual/recurrent tumour; only hearing ear; bilateral; age	Royal Hallamshire Hospital, UK	Not reported 18/27 with useful hearing prior to treatment	Hearing: Gardner–Roberston	Tumour control: 6/29 regression; 17/29 stable; 6/29 progression tumours < 3cm diam better control	*Facial Nerve:*9/27 developed facial palsy (2 transient); 9/24 in those with prior normal function *Trigeminal nerve*: 5/27 developed trigeminal neuropathy; 5/25 in those with prior normal function *Hearing (G–R):* 9/27 retained useful hearing at 4yrs; 18 patients had useful hearing prior to SRS, 9/18 retained	?? comparability to other studies as patients treated before 1990 Results are also presented split by treatment dose

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up: type and % patients	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Kobayashi et al. 1994)	n=40 /44 tumours mean age 53; 16M, 28F n=4, NF–2; n=10 prior surgery; n=34 initial treatment	GK	Retrospective review May 1991 – Dec 1992	Komakai City Hospital, Japan	Not reported 21/44 with some hearing prior to treatment 23/44 were deaf	Not reported	Not reported in usable fashion	*Facial Nerve*: new or worse 7/44 (4 improved with treatment with steroids 1 pre-existing improved *Trigeminal nerve*: 3/44 new or worse, 1 pre-existing improved *Hearing*:21 patients had some hearing at time of SRS (23 deaf): remained unchanged in 9/21; improved 1/21; deteriorated 11/21; 2/44 perifocal oedema; 2/44 hydrocephalus requiring shunt	
(Noren et al. 1993)	n=254 tumours n=61 NF-2 (bilateral)	GK	Retrospective review 1969–91	Karolinska Hospital	Minimum follow-up 12 months mean 54 (12–206) MRI evals 132/154 with some hearing (I–III) prior to treatment	Facial nerve function: House–Brackmann (HB)	Unilateral 55% regression, 33% stable; 12% progression Bilateral NF-2 33% regression; 43% stable; 24% progression unclear at what time point??	*Facial Nerve*: new or worse 17%: 6% mild HB2–3; 7% moderate HB4; 4% severe HB5–6 *Trigeminal nerve*: new or worse19%: 12% slight; 3% moderate; 4% severe *Hearing*: 132 patients with loss < 90dB PTA loss (GR I–III) 22% no change; 55% slight – mod further loss; 23% severe or total loss; 8% Peritumoral oedema; 3% shunting due to CSF disturbance	Results split into unilateral and bilateral/NF-2 type Fig 2 indicates tumour change over time, but no values on graphs

Table 41 LINAC treatment of acoustic neuroma

1 Gamma Knife, LINAC, unspecified
2 selected, consecutive, referred, retrospective, unspecified

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up: type and % patients	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Tomasevic et al. 1998)	N=31 (34 tumours) Mean age 44 (17–76) N=12 recurrent N=22 initial Mean diameter 23mm (10–43)	LINAC	Retrospective March 1991 – Aug 1996	Prince of Wales Hospital, Sydney	27 ≥ 6mo f/up	Not reported	22/27 (81%) < 50% reduction in size 3/27 (11%) > 50% reduction in size 1/27 (4%) complete cure	New or worsening symptoms Hearing 9 (26%) Facial nerve 8 (24%) Trigeminal nerve 6 (18%) Disequilibrium 5 (15%) Tinnitus 1 (3%) Hydrocephalus 1 (3%)	Mean follow-up 32 mo (0–65) 2 patients died of unrelated causes, 2 lost to follow up 3 patients insuf-ficient follow-up yet complication rate independent of prior microsurgery
(Mendenhall et al. 1996)	N=56 N=4 NF-2	LINAC	Retrospective series July1988 – Nov 1994	University of Florida	MR/CT avail in 93% pts Radiograph follow up at 3yrs n=15, 5yrs n=4 Clinical follow up at 3yrs n=20, 5yrs n=8	Local control tumour regression without evidence of regrowth or stable disease	27 patients had imaging at 2 years: regression in 19/27 (70%); stable in 8/27 (30%); 5 year local control rate based on imaging was 93% for the 52 patients with MR/CT	13 patients developed new or worsening complications n=7 new trigeminal or facial palsy n=5 worse trigem or facial palsy n=3 hydrocephalus	Trigeminal and facial neuro-pathies not specified individually
(Valentino and Raimondi 1995)	N=23 (24 tumours) (13M, 10F) mean age 52 (19–77) N=5 NF-2 N=7 recurrent N=16 initial	LINAC	1984–93 1560 SRS, 27 acoustic neuroma; 23 patients w/ follow-up ≥ 2yrs (mean 3yrs 4mo range 2–8 yrs)	Clinical Flaminia, Rome	Follow-up ≥ 2yrs (mean 3yrs 4mo range 2–8 yrs	Tumour response based on volume changes	9/24 (%) regressed 14/24 (%) stable 1/24 (%) progressed	Pre-RS abnorm / N / Improved / No change / worse Hearing deficit: 18 / 2 (9%) / 16 / 0 Vestib symptom: 12 / 3(25%) / 8 / 1 Facial palsy: 12 / 5 (42%) / 6 / 1 Trigem neurop: 8 / 3 (37%) / 4 / 1	N=2/24 had subsequent surgery

Table 42 Fractionated stereotactic radiotherapy treatment of acoustic neuroma

1 Gamma Knife, LINAC, fract = fractionated dosing
2 selected, consecutive, referred, retrospective, unspecified

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up (type and % patients)	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Poen et al. 1999)	N=33 (34 tumours); 21M 12F Mdn age 50 (22–88) N=10 NF-2 27 tumours untreated; 7 recurrent/ progressive Median diam 20mm (7–42) 31 pts (32 tumours) evaluable	Fract LINAC (3 fractions of 700 Gy over 24hrs)	Assume consecutive, retrospective August 1994 – January 1998	Stanford University Medical Centre	Radiographic follow-up on all 31 patients (32 tumours) 21/33 with some hearing (GR I–III) 13/33 with useful hearing (GR I–II) prior to treatment	*Trigeminal:* any paresthesia/anesthesia in trigem distrib. *Facial nerve function:* House–Brackmann (HB) *Hearing:* Gardner–Roberston (GR); PTA Progression ≥3mm increase; regression ≥ 3mm decrease in any dimension Stable < 3mm change in all dimensions	Regression in 11/32 (34%) Stabilisation 20/32 (63%) Progression 1/32 (3%) (NF-2) 2 year actuarial probability of FFP 93%	Trigeminal injury 5/31 (16%) mdn 6mo after RS (3 new, 2 worsening) Facial nerve injury 1/31 (3%) (HB III) @ 7mo transient vertigo 2/31 (6%) Hearing preservation: Functional hearing diminished gradually over follow-up: for patients with serviceable (GR I–III)(n=21) 2yr actuarial probability of maintaining serviceable hearing was 81%; GR I–II (useful) (n=13) 77% maintained useful hearing (mdn f/up 2 yrs); 13/13 maintained some hearing (I–III)	Tumour = 20mm assoc with a trend towards trigeminal injury (p=0.16) NF-2 assoc. with poorer hearing preservation
(Shirato et al. 1999)	Fractionated SRT: n=50 (21M, 29F) 37 initial tx, 13 rrecurrent) Mean age 52 (14–82) 2 NF-2 pts MRI Obs only n=27 (Mean age 57)	Fract SRT and observat'n only	Unclear perspective; two patient groups: Fractionated SRT 1991–97 (= 35 mm diam) and MRI observation only (too old for surgery, no major symptoms 89–97)	Hokkaido University, Sapporo Japan	MRI every 6 mo	*Tumour growth speed:* (max tumour size at last f/up – max tumour size at presentation)/f/up months)/12 *Hearing*: Gardner–Roberston; PTA	Actuarial tumour control of SRT significantly better than obs (p< 0.0001) 8 SRT patients had progression (6 transient); 1 had surgery 11 (41%) Obs patients had salvage therapy (surgery or SRT) ≥ 21mo from initial presentation Tumour growth 3.87mm/yr (obs) – 0.75mm./yr (SRT)	No permanent facial or trigem neuropathy in SRT group Transient facial nerve palsy in 5%; transient trigem palsy 12% Actuarial G–R class preservation rates 3yr 61% (obs group) 53% (SRT group) 5 yr 31% (obs group) 53% (SRT group)	Significant correlation between slow growth rate and improved hearing preservation rates (r=0.51)
(Lederman et al. 1997)	N=38 (39 tumours) Mean 60 yrs(35–89)	Fract SRT	Nov 1993 – July 1996 consecutive patients mean tumour diam 2.7cm (0.6–5.0) Results grouped by tumour size (< 3cm diam vs = 3cm diam)	Staten Island University Hospital, NY	Median MRI f/up 18 mo (4–30 mo) Median clinical follow-up 24 mo (4–32 mo) PTA is available in 32/38	Not reported PTA 32/38 patients	*All patients(38):* 69% tumour regression; 31% stabilisation *< 3cm diameter (23):* 61% regression; 39% stabilisation *³ 3cm diameter (15/16 tumours*): 81% regression; 19% stabilisation	*All patients (32):* PTA: 12% improved, 81% stable; 7% worsened No new permanent trigeminal or facial neuropathy; 2 preexisting improved 1 transient facial palsy *< 3cm diameter (21):* PTA 9% improved; 86% stable; 5% worse *³ 3cm diameter (9):* PTA 18% improved; 73% stable; 9% worse	

1 Gamma Knife, LINAC, fract = fractionated dosing
2 selected, consecutive, referred, retrospective, unspecified

Study	Patients: N, source, history	Type of SRS[1]	Perspective[2]	Hospital	Follow-up (type and % patients)	Measurements	Efficacy outcomes	Safety outcomes	Comments
(Varlotto et al. 1996)	N=12 mdn age 45 (27–70) N=8 initial treatment; 4 recurrent	Fract LINAC	June 1992 – Oct 1994 Mdn follow-up 26.5mo (16–44); < 5cm diam; KPS > 70; informed consent	Harvard Medical School	Radiographic and neurological follow-up avail for all pts 9/12 with useful hearing prior to treatment	Not reported	25% regression; 75% stabilisation at 26.5 months follow-up	9/12 patients had useful hearing before SRT; all retained useful hearing; 1/9 mild decrease & 1/9 mild improvement. No new facial or trigeminal neuropathies at 26.5 mo median follow-up: 5 remained normal; 2/7 pre-existing improved	One patient had a craniotomy at 29 mo for persistent headache (related to SRT and previous surgery)
(Andrews et al. 1995)	N=26 (27 tumours) Mdn age 65.5 (21–91) 19 tumours initial; 8 recurrent n=3 NF-2	Fract LINAC	Prospective Phase II Aug 1992 – June 1995 nonoperative only	Temple University Health Centre and Wills Neurosurg. Institute	7/26 with serviceable hearing prior to treatment	Trigeminal nerve function Tested by pinprick and corneal reflex Facial nerve function: House–Brackmann (HB) Hearing: Gardner–Roberston (GR); PTA	Radiographic stability or regression seen in all serially evaluable tumours. For patients with follow-up >12 months, a statistically significant decrease in volume over time was seen in 8 evaluable patients. (–6.5% per month)	3/23 (13%) new trigem neuropath 2/7 (29%) new hearing deficit (pts with serviceable pretreatment hearing) 5/7 maintained serviceable hearing 0/22 (0%) new facial neuropathy 2/26 (8%) nausea 4/26 (15%) gait ataxia 6/26 (23%) dizziness 7/26 (27%) scalp pain 2/26 (8%) hydrocephalus	v. clear inclusion criteria prospective phase II trial with informed consent

Appendix D – Hearing Classification Scales

Table 43 Gardner–Roberston hearing classification system

Auditory Grade	Hearing level	Pure tone average/tonal loss (dB)	Speech discrimination score (%)
I	Good	0–30	70–100
II	Serviceable	31–50	50–69
III	Nonserviceable	50–90	5–49
IV	Poor	91 max	1–4
V	None	Non-testable	0

Source: (Gardner and Robertson 1988).

Table 44 AAO–HNS hearing classification system

Class	Pure tone thresholds	Speech discrimination score (%)
A	≤ 30dB	≥70
B	>30dB, ≤50dB	≥50
C	>50dB	≥50
D	Any level	<50

Source: (American Academy of Otolaryngology - Head and Neck Surgery 1995).

Table 45 Norstadt hearing classification system

Audiometric hearing classification		Classification of speech discrimination	
Class	Hearing (dB)	Class	Discrimination (%)
A1	Good hearing, 0–30	D1	Normal discrimination, 100–95
A2	Fair hearing, 31–60	D2	Good discrimination, 90–70
A3	Bad hearing, 61–90	D3	Fair discrimination, 65–40
A4	Functional deafness, 91–120	D4	Bad discrimination, 35–5
A5	Deafness, > 120	D5	Lost discrimination, 0

Source: (Samii and Matthies 1997b).

Table 46 Hannover hearing classification system

Class	Hearing	Audiometry (dB)	Speech discrimination score (%)
H1	Normal	0–20	100–95
H2	Useful	21–40	95–70 or better
H3	Moderate	41–60	65–40 or better
H4	Poor	61–80	35–10 or better
H5	No functional hearing	>80	5–0 or better

Source: (Samii and Matthies 1997b).

Table 47 Shelton hearing classification system

Class	Criteria	
	Speech reception threshold (dB)	Speech discrimination score (%)
Good	≤ 30	> 70
Serviceable or better	≤ 50	> 50
Measurable	Any measurable hearing	

Source: (Shelton C. and Hitselberger 1991)

Both Speech reception threshold (SRT) and Speech discrimination score (SDS) criteria of a class must be met.

Appendix E – HTA Reports for Radiosurgery

English Language Health Technology Assessment Reports

ANAES (2000) Evaluation clinique et economique de la radiochirurgie intracranienne en conditions stereotaxiques (Economic and clinical evaluation of intracranial radiosurgery in stereotactic conditions). pp.1-75. Agence Nationale d'Accredititaion et d'Evaluation en Sante (ISBN 2-910653-82-X).

AHTAC (1991) Stereotactic radiosurgery in Australia: proposals for nationally funded centres.

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CCOHTA (1992) Stereotactic Radiosurgery. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

ECRI (1996) Stereotactic Radiosurgery for Intracranial Tumors and Arteriovenous Malformations Executive Briefing No. 45. ECRI.

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Hailey, D., Conway, L. and Dankiw, W. (1990) Options for stereotactic radiosurgery. A Discussion Paper.

Minnesota Health Technology Advisory Committee (1995) Stereotactic radiosurgery: neurological applications.

Oregon Health Resources Commission (1997) Technology Assessment & Health Resources Plan: Stereotactic Radiosurgery.

Schneider, W.L. and Hailey, D. (1998) Stereotactic radiosurgery: options for Albertans. The Alberta Heritage Foundation for Medical Research.

Schneider, W.L. and Hailey, D. (1999) Treatment options for acoustic neuroma. The Alberta Heritage Foundation for Medical Research.

University HealthSystem Consortium (1995) Stereotactic radiosurgery (Technology Report). pp.1-58. Oak Brook, Illinois: University HealthSystem Consortium.

Foreign Language Health Technology Assessment Reports

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Ongoing Health Technology Assessment Projects

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CETS Radiosurgery with LINAC and Gamma Knife, systematic review (French - Canada) (Ongoing Project). Montreal, Quebec, Canada: Conseil de Evaluation des Technologies de la sante (CETS).

Appendix F – HTA Conclusion Summary

Conclusions from the larger most recent methodologically sound health technology assessment reports are reproduced in full within this appendix. Some conclusions drawn by reports are not applicable to Australia as they refer specifically to health care arrangements and recommendations for the country of report origin. Where such conclusions have been drawn, it will be noted below, however the full recommendation will not be cited.

Report Title	Conclusions/Recommendations
ANAES (2000) Economic and clinical evaluation of intracranial radiosurgery in stereotactic conditions	**Clinical data – Conclusions (page 34)** ▪ Clinical results presently available come mainly from retrospective studies based on series of non-controlled cases ▪ Efficiency criteria of the treatment differ according to the study, description of patients is incomplete and latent period between treatment as well as evaluation of the results is variable. The period of time is sometimes insufficient, in particular for some pathologies like slow evolution neurinoma and meningioma ▪ level of proof of these studies is therefore low ▪ the use of apparatus differs depending on the pathology being treated, and the 'operator dependent' nature of the technique is an important factor of inconsistency in the series ▪ currently, critical analysis of the literature, pathology by pathology, does not allow to establish a reliable comparison between conventional neurosurgical procedures and SRS and between the two types of equipment, the gamma knife and the linear accelerator ▪ The evaluation of efficiency [?efficacy] and security [?safety] of SRS…will only be possible with controlled randomised studies, comparing different strategies, with sufficient number of patients and with prior determination of clear criteria for judgement. Studies with a prolonged follow up period would be necessary in order to determine which specific groups of patients benefit most from this procedure ▪ In France, SRS is already offered as first choice of treatment for Schwannoma of grade II and III and for certain AVMs situated in a functional and / or deep zone. For the later, it appears difficult: — to propose a neurosurgical treatment to patients, considering the encouraging results of the SRS procedure in terms of the efficiency and security; — to build up a protocol for a study comparing SRS and microsurgery in these pathologies. ▪ In other cases, in particular grade II and III Schwannoma, no current data allows reconsideration of the pertinence of the clinical trials comparing microsurgery to SRS by gamma knife and to SRS by dedicated linear accelerator; in the United States such comparative trials have begun for the treatment of Metastasis. ▪ Considering the technical improvement of the linear accelerator, a prospective and randomized comparative evaluation of SRS by dedicated linear accelerator versus SRS by gamma knife should be envisaged for all the pathologies likely to benefit from this technology. **Overall conclusions and recommendation (pages 46-48)** ▪ Stereotactic radiosurgery was introduced in France between 1968 and 1992. The progressive development of the centers carrying out this type of treatment resulted in 925 therapeutic acts in 1998. In 1999, Stereotactic Radiotherapy was available in 17 centers. 1 center uses a gamma knife and 16 use adapted linear accelerators. There is no dedicated linear accelerator in France. ▪ The different types of equipment are used according to pathology; up to now the linear accelerator has been little used in the treatment of Vestibular Schwannoma and tumors of the base of the skull, these pathologies being treated by gamma Knife. ▪ Most studies available [for these indications] relate to the use of the gamma knife. They do not

	help in the comparison of the efficiency of stereotactic radiosurgery against other therapeutic options, or the superiority of one of the techniques (gamma knife, adapted linear accelerator and dedicated linear accelerator)… ▪ Considering the weak value of available studies in terms of clinical efficiency, the value of economic studies is only an indicative one. The analysis of the respective costs of using gamma knife and adapted linear accelerator are of little help in defining a potential economic advantage in favor of one or the other technique… ▪ Nevertheless, the economic data presently available allows the definitions of the number of treated patients per year beyond which the use of one technique is more appropriate than the other. The costs of each treatment would help to choose between the gamma knife and dedicated linear accelerator if the number of treatment per year is high, or the adapted linear accelerator if this number is low. ▪ This data is to be considered with caution due to the difficulty of transposing foreign data to the French market, and the lack of French data on the subject. ▪ Stereotactic radiosurgery is now the alternative to microsurgery in the treatment of acoustic neurinoma, cerebral metastasis, meningioma of the base and arterio-venous malformations. It is the only treatment available for AVMs located in functional and/or deep areas. At this point in time, there is no data relating to the following: — the number of patients suitable for a gamma knife treatment; — the number of sites necessary to treat all these patients, whilst carrying with the development of the technology — the type of equipment to use (gamma knife or Linear accelerator); — the best type of management ▪ *[Two (2) additional conclusions specific to the French health care environment and provision of services]* ▪ The results of SRS treatments have to be evaluated: — The development of clinical research has to be given priority to procure a prospective comparison of dedicated systems…in terms of efficiency [?efficacy] and security [?safety] of the treatment of patients eligible for this therapy — The new indications of SRS have to be considered as experimental surgery. They have to be prospectively studied and in the same way in order to validate their pertinence prior to wider use — The same applies to other modalities of stereotactic irradiation, such as fractionated irradiation — The clinical evaluation coupled with a measure of the associated direct and indirect costs would allow for the provision of criteria to choose one or other techniques according to the defined needs of the centres
Schneider, W.L. and Hailey, D. (1999) Treatment options for acoustic neuroma. The Alberta Heritage Foundation for Medical Research.	**Summary** ▪ Available treatment options for persons with acoustic neuroma are microsurgery, stereotactic radiosurgery (SRS) and watchful waiting. ▪ Microsurgery is the primary treatment option for acoustic neuroma. Surgical techniques continue to evolve. ▪ Surgical removal of these tumours requires considerable expertise to maintain low morbidity and mortality rates. ▪ There is evidence, from methodologically weak studies, that SRS is efficacious in treatment of acoustic neuroma in suitably selected individuals. ▪ Evidence on the comparative effectiveness of SRS and microsurgery remains limited. ▪ Both SRS and microsurgery have associated short-term and long-term complications. Unlike SRS, microsurgery will require post-operative hospital stay and subsequent convalescence. ▪ There is no evidence of any difference in effectiveness between the LINAC and gamma knife approaches to SRS.

	▪ The overall performance of SRS will depend on the expertise of the patient management team and the quality of imaging and treatment planning, rather than the method used to deliver radiation. ▪ Watchful waiting is preferred for older persons with slow growing tumours. ▪ Regardless of the modality of treatment, it is imperative that patients be referred to centres of excellence. These would be centres that treat large numbers of patients with acoustic neuroma. **Discussion** ▪ The present assessment has similar findings to those in earlier HTA reports that have considered treatment of acoustic neuroma by SRS. In summary: ▪ There is evidence that SRS is efficacious in the treatment of acoustic neuroma in suitably selected individuals. However, all studies have methodological weaknesses. There are no RCTs of SRS in comparison with other forms of treatment. ▪ There is also evidence that SRS has adverse effects in a proportion of patients who are treated for this condition. ▪ Comparative data with surgical outcomes have some limitations. ▪ Microsurgery will remain the primary option for many individuals with acoustic neuroma. ▪ There is no convincing evidence that either the gamma knife or the LINAC versions of SRS is superior to the other in terms of patient outcomes. ▪ A further point is that there are continuing, significant developments in surgical procedures for acoustic neuroma.
Schneider, W.L. and Hailey, D. (1998) Stereotactic radiosurgery: options for Albertans. The Alberta Heritage Foundation for Medical Research.	**Summary** ▪ SRS has been most widely used in the treatment of brain metastases, arteriovenous malformations (AVMs) and acoustic neuromas. ▪ The two most common approaches to SRS use the Gamma knife (GK) or focused linear accelerator (LINAC). Each delivers a focused beam of radiation to a tumour or malformation. ▪ The report confirms findings from other assessments that: ▪ the quality of the available evidence on SRS effectiveness is limited; ▪ there is insufficient information to determine the comparative effectiveness of the GK and LINAC approaches; ▪ data on comparison of SRS with other types of treatment are also limited; ▪ the GK approach is more expensive than that using the LINAC; ▪ excellent quality assurance and placement of SRS in specialized centres are essential. ▪ The role of SRS in treatment of brain metastases is still not well defined. It appears to have a place in the management of appropriately selected patients, and is a useful option when the patient is not a candidate for surgery. ▪ SRS for AVMs may be appropriate for selected patients and a good option for those who are not eligible for surgery. Long term follow-up is required, however, to monitor for delayed radiation effects. Surgery remains the preferred option for most cases. ▪ SRS has a place in the treatment of acoustic neuroma. However, surgery or observation are management options for many patients. The literature is unclear regarding complications and retention of useful hearing following surgical and SRS procedures. ▪ *[Four (4) additional conclusions specifically relating to the provision of services and health care environment in Alberta, Canada]* **Discussion** ▪ The review of the literature and the discussions held with health care professionals during development of this report have confirmed several conclusions that have been reached by other agencies in earlier assessments. ▪ SRS is a useful technology in the treatment of a number of neurological conditions. However, the quality of the evidence of effectiveness, particularly in terms of long-term outcomes, remains limited. Decisions on whether to refer individual patients for SRS will continue to require careful consideration of history and diagnostic findings by the specialists concerned.

	The role of SRS in relation to surgery still does not seem well defined in relation to treatment of AVMs and acoustic neuroma. Microsurgery will remain a major option for patients with these conditions. ▪ The evidence of benefit from SRS treatment of brain metastasis remains limited. It seems clear that significantly worse outcomes are obtained in cases where more than two metastases can be identified. There are indications of good local control, and improvements to quality of life through increased functional independence. Effects on survival are less clear. With all outcomes, the basis for comparison with other approaches to treatment is weak. ▪ Both the GK and LINAC approaches to SRS continue to be widely used. There is no evidence that either one is more effective than the other. Given the substantially higher costs of the GK approach, only referral to good quality LINAC SRS facilities should be considered for patients in Alberta. ▪ Excellent quality assurance, expertise in advanced diagnostic imaging and planning and involvement of a multi-disciplinary team of health professionals are essential for an SRS facility. ▪ *[Two (2) additional conclusions specifically relating to the provision of services and health care environment in Alberta, Canada]*
Anderson, D. and Flynn, K. (1997) Stereotactic radiosurgery for metastases to the brain: A systematic review of published studies of effectiveness. 7, VA HSR&D.	**Conclusions** ▪ In the absence of data from high quality studies, uncertainty remains about the true effectiveness of SRS for the treatment of metastases to the brain. One randomised clinical trial is in progress, and further trials are need, to address the many unanswered questions about the use of SRS for this application. Such trials will provide stronger evidence on which to base clinical and policy decisions
AETS (1997) Stereotactic radiosurgery: indications and situation in Spain (Spanish with English summary).	**English Executive summary conclusions** ▪ The effectiveness of the two most used stereotactic radiosurgery systems (gamma knife and Linear Accelerator) in the treatment of arteriovenous malformations and tumors is similar, although insufficient information is available on several of the indications to compare the effectiveness of these two means of treatment. ▪ In most indications, the alternatives to radiosurgery are neurosurgical procedures that require a craniotomy (conventional surgery or microsurgery), and may also use the stereotactic techniques. Neurosurgery, microsurgery and external conventional radiotherapy are still the main methods used in the treatment of brain lesions and are the main reference for result comparison of the radiosurgical techniques. Whether stereotactic equipment is used or not, surgical resection of a brain lesion is risky for the patient (anesthesia risks, general surgical complications and the possibility of damaging normal brain tissue or the neural components), and higher costs (longer hospitalization periods). ▪ Evaluations of the results of radiosurgery are limited by several issues,: poor quality of the evidence provided by the studies carried out (mainly description of a number of cases), incomplete description of all the patients treated, heterogeneity of the studies with regard to selection of cases, definition of therapy success or failure and duration of the latency period from the time of treatment of the measurement of the result. **Recommendations** ▪ Stereotactic radiosurgery is undergoing rapid development and is an emergent technology that is extending the fields of application and demands continuous assessment, specially as regards long term results. Protocols and standards of the stereotactic radiosurgery procedures and evaluation methods will advance the knowledge on the efficiency and effectiveness in the different fields. The systematic recording for each phase and concerning the application and results of the stereotactic radiosurgery, will facilitate the evaluation process. Significant uncertainties remain in each one of the revised indications, especially in the case of the metastases and functional treatment.

Appendix G – Review protocols

Cerebral arteriovenous malformations

Objectives

To conduct systematic reviews addressing the following questions:

Question no.	Selection criteria			
	Patients	**Intervention**	**Comparator**	**Outcomes**
1	Patients with AVMs in whom intervention is indicated, eg those with a previous bleed or 'expanding' haematoma or progressive neurological deficit	Stereotactic radiosurgery with gamma knife	Stereotactic radiosurgery with LINAC	See below
2	Patients with cerebral AVMs in whom previous intervention has been unsuccessful in achieving complete obliteration	Stereotactic radiosurgery with gamma knife	Stereotactic radiosurgery with LINAC	See below
3	Patients with cerebral AVMs in whom previous intervention has been unsuccessful in achieving complete obliteration	Stereotactic radiosurgery	Neurosurgery	See below
4	Patients with cerebral AVMs in whom intervention is indicated, eg those with a previous bleed or 'expanding' haema-toma or progressive neurological deficit	Stereotactic radiosurgery	Neurosurgery	See below

Primary outcome measures

1. Survival
   - Event free
2. Obliteration
   - Imaging evidence of obliteration (angiogram)
3. Intracranial haemorrhage
   - recurrent
4. Therapeutic index
   - Response rate (successful obliteration) : rate of radiation induced complications

Secondary outcome measures

5. Procedural success
   - Morbidity / complications
   - Mortality
6. Quality of life
   - Short term
   - Longer term
   - Symptoms of disease: e.g. seizure, headache, neurological deficit
7. Safety
   - Short term side effects of treatment
   - Long term radiation complications
8. Cost

Subgroups

The following subgroups may be considered:

- age (younger / older): <40 vs ≥ 40 years of age
- risk of haemorrhage (low / intermediate / high)
- rebleed rate (have bled once or more / have not bled)
- lesion size (smaller / larger): <4cm vs ≥ 4 cm
- endovascular embolisation

Exclusion criteria

- Angiographically occult vascular malformations (AOVMs)
- Venous angioma
- Low/high flow carotid cavernous fistulae
- Cerebral cavernous malformation

Cerebral metastases

Objectives

To conduct systematic reviews addressing the following questions:

Question no.	Selection criteria			
	Patients	**Intervention**	**Comparator**	**Outcomes**
5	Patients with brain metastases (single or multiple lesions) who are suitable for stereotactic radiosurgery	Stereotactic radiosurgery with gamma knife	Stereotactic radiosurgery with LINAC	Survival Control of lesion/freedom from progression Quality of life Short-term Longer-term symptoms of disease side effects of treatment Cost
6	Patients with brain metastases (single or multiple lesions) who are suitable for stereotactic radiosurgery	Stereotactic radiosurgery plus WBRT	WBRT alone	As above
7	Patients with brain metastases (single or multiple lesions) who are suitable for stereotactic radiosurgery	Stereotactic radiosurgery plus WBRT	Stereotactic radiosurgery alone	As above

Subgroups

The following subgroups may be considered:

- lesion size
- number of lesions (single lesion or multiple lesions with single focus vs multiple lesions without focus)
- baseline neurological status: symptomatic or not
- baseline performance status (e.g. Karnofsky >=70 or <70)
- evidence of extracranial disease (e.g. present or absent)
- tumour type: e.g. lymphoma or germ cell tumour vs breast vs other
- Active/inactive disease outside CNS
- Prior therapy (Surgery, whole brain radiotherapy, chemotherapy or no treatment)

Exclusion criteria

- Brachytherapy or interstitial radiotherapy/interstitial radiosurgery have been excluded

Acoustic neuroma

Objectives

To conduct systematic reviews addressing the following questions:

Question no.	Selection criteria			
	Patients	**Intervention**	**Comparator**	**Outcomes**
8	Patients with an acoustic neuroma who have received surgery	Stereotactic radiosurgery with gamma knife	Stereotactic radiosurgery with LINAC	Hearing Cranial nerve abnormality Local control Other complications, eg oedema or haemorrhage
9	Patients with an acoustic neuroma who are unsuitable for surgery	Stereotactic radiosurgery with gamma knife	Stereotactic radiosurgery with LINAC	As above
10	Patients with an acoustic neuroma	Stereotactic radiosurgery	Surgery alone	As above

Abbreviations

^{60}Co	Cobalt-60
AN-DRG	Australian National Diagnosis Related Groups
AOVM	Angiographically occult vascular malformation
AVM	arteriovenous malformation
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computerised tomography
DARE	Database of Abstracts and Reviews of Effectiveness
dB	decibel
EED	Economic Evaluation Database
FFP	Freedom from Progression
G–R	Gardner–Robinson Scale of Hearing Classification
HTA	Health Technology Assessment
KPS	Karnofsky Performance Score
LINAC	linear accelerator
MDRC	Management Decision and Research Centre (US Department of Veterans' Affairs)
MeSH	Medical Subject Headings
MRI	magnetic resonance imaging
MSAC	Medicare Services Advisory Committee
NF-2	Neurofibromatosis-2
NHMRC	National Health and Medical Research Centre
NHS	National Health Service (UK)
PDQ	CancerNet Physician Data Query
QALY	quality adjusted life years
QOL	Quality of Life
RCT	randomised controlled trial
RS	radiosurgery
SRS	stereotactic radiosurgery
UCSF	University of California (San Francisco)
VA TAP	Veterans' Affairs Technology Assessment Program
WBRT	whole brain radiotherapy

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