Alberta Heritage Foundation
for Medical Research

Stereotactic radiosurgery: options for Albertans

Wendy L. Schneider and David Hailey

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome, and should be sent to:

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Contents

Summary

- This report has been prepared in response to a request from Alberta Health in reference to referral of patients outside the province for stereotactic radiosurgery (SRS) treatment.

- 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.

- The potential SRS caseload for Alberta is uncertain, but might be 30 to 50 per year.

- The cost of treating a patient from Alberta with GK SRS in the U.S.A. is approximately $30,000. For LINAC SRS treatment in Ontario the cost could range from $8,000 to $11,000. As there is no evidence that there is any difference in effectiveness between GK SRS and LINAC SRS there is no reason to send patients to the U.S.A.

- An Alberta-based SRS facility might cost about $4,000 per case, at a caseload of 30 per year.

- If SRS is introduced in the province of Alberta it should be limited to one site, given the small caseload and the need to develop and maintain expertise.

Introduction

Stereotactic radiosurgery (SRS) is a non-surgical technique which utilizes ionizing radiation to treat intracranial lesions. Approximately 28,000 patients have been treated using this approach since 1968 (3,37). SRS is used as primary treatment, or as an adjunct to other therapy for certain types of neurological disorders including arteriovenous malformations (AVMs), acoustic neuromas, and brain metastases.

In SRS the radiation beam is more focused than is the case with radiotherapy, so that the lesion can be accurately targeted and irradiated while sparing normal tissue. Two approaches to SRS have been commonly used. In the first of these, a device known as the Gamma Knife® (GK) delivers focused gamma radiation from an array of cobalt-60 sources. In the second, a conventional linear accelerator (LINAC) is modified by the addition of a collimator to provide a focused x-ray beam for treatment of the lesion (46). With both approaches, diagnostic imaging and extensive therapy planning are used to define the lesion and the volume which is to be irradiated. Proton beam therapy has also been used in stereotactic radiosurgery, but is not considered here.

The present report has been prepared following a request by Alberta Health in relation to referral of patients outside the province for treatment with SRS. There was interest by the department in the comparative effectiveness of the two main approaches to SRS (GK and LINAC) and in the current status of the technology. In addition, the opportunity has been taken to consider cost and organizational issues related to the provision of SRS services for Alberta, either within the province or through referral elsewhere.

Reports on the use of SRS have appeared in the literature over many years, but there are limitations in the scope and quality of the studies that have been undertaken. Notable features are the absence of comparative studies of the GK and LINAC approaches, and the still limited evidence from good quality trials of the effectiveness of either method.

There have been several previous reports on SRS by health technology assessment agencies, including brief advice from AHFMR on application to metastatic melanoma (2). Table 1 summarizes conclusions reached in earlier assessments. Points made in several of the reports include:

- The quality of the available evidence on SRS effectiveness is limited.
- There is insufficient information to compare the effectiveness of the GK and LINAC approaches.
- Comparison of SRS with other approaches is also limited.
- The GK approach is more expensive than the LINAC.
- Excellent quality assurance is necessary.
- Placement of SRS in specialized centres is essential.

In the present report, emphasis has been placed on appraisal of the recent literature, in order to obtain any significant information that has emerged since completion of the earlier assessments. The methodology used is outlined in Appendix A.

Table 1: Previous health technology assessments of stereotactic radiosurgery

Agency	Conclusions
Australian Institute of Health (27) February 1990	• Cost/effectiveness advantage over invasive surgery for some patients with AVMs or benign tumours • LINAC has potential to meet/exceed the GK capabilities Issues: • Proven record of the gamma knife • Greater flexibility, lower cost of LINAC • Need for assurance on the reproducibility, effectiveness and safety of LINAC • Continuing rapid development of focused LINAC methods • Availability of commercial systems (implies regulatory agency approval for devices) • Availability of existing expertise using focused radiation • Capacity of existing radiotherapy services
Australian Health Technology Advisory Committee (7) October 1991	• Suitable SRS sites are hospitals with appropriate expertise • Advised against ad hoc SRS facilities • Patient numbers will initially be low for SRS so use of existing LINACs for SRS would increase overall utilization • Application of SRS to malignant disease would increase use
Health Council of the Netherlands: Committee on Stereotactic Radiotherapy (28) October 1994	• SRS is an emerging technology past the experimental stage • Unknown whether SRS is more effective than standard treatment modalities • Studies not randomized, involved small numbers of patients • SRS is useful when AVMs are inaccessible for resection or when the patient cannot risk surgery • Not enough evidence to support SRS over surgery or conventional radiotherapy • There are provisional indications that SRS has a favourable influence on the quality of life

Table 1 (continued)

Minnesota Health Care Commission, Health Technology Advisory Committee (29) June 1995	• SRS appears to be a safe and effective treatment for certain carefully selected patients • Long-term studies are required to investigate the incidence of radiation-induced carcinomas and other long-term complications • Insufficient evidence regarding the clinical superiority of GK versus LINAC SRS • SRS for AVM should not be considered as an alternative to microsurgery in patients judged suitable for surgery • Benign intracranial tumours are well-suited for SRS • Conventional surgery still indicated in young, healthy patients with acoustic neuroma • SRS is frequently attempted in those who have failed radiation/chemotherapy or in those for whom surgical excision is not possible • SRS should be considered only as part of treatment regime • Patients with metastatic tumours show improved neurological functioning/median survival time after SRS • Those patients receiving radiation therapy and SRS had significantly better local tumour control than patients receiving SRS alone. Survival time was not affected • SRS was deemed advantageous in terms of low incidence of side effects, and shortened hospitalization
ECRI (17) February 1996	• There is no evidence that one SRS method is superior to the other • Little evidence is available on which to base any comparison of the effectiveness of GK and LINAC SRS for the control of brain tumours • SRS for acoustic neuromas provides high rates of short-term tumour control. No long-term studies have been done, and it is not possible to determine whether SRS prevents tumour recurrence • Poor methodology of studies makes it impossible to prove that SRS preserves hearing in the affected ear more often than conventional surgery. • The clinical data are insufficient to determine the effectiveness of SRS for meningiomas • Combined SRS and WBRT have yielded longer survival times than WBRT alone, however, there are insufficient clinical data from which to draw conclusions about the comparative effectiveness of SRS and conventional surgery • Efficacy of SRS for primary malignancies has not been demonstrated
AHFMR (2) February 1997	• There is evidence that SRS is helpful in the management of brain metastases, often in association with other forms of treatment. • Benefits include local control and improvement of symptoms. • Effects on survival are less clear, with little comparative data for surgery. • Patient selection criteria require further development. • Role of SRS in management of metastatic melanoma, and treatment outcomes, require further validation.

Table 1 (continued)

Oregon Health Resources Commission (40) June 1997	• Overall GK and LINAC show comparable effectiveness • Evidence for comparing effectiveness of GK v. LINAC not strong enough for definitive conclusions and recommendations • LINAC SRS is a cost-effective modality relative to GK SRS • GK, a dedicated device used solely for SRS, has greater potential for unused excess capacity • To assure safety, quality and efficiency, SRS should only be performed in specialized hospitals • Concentrating SRS facilities to a few sites assures quality • No GK facility should be introduced into Oregon • Establishment of a cooperative registry/data base of SRS cases and outcomes, common data collection, definition protocols across the providers, pool data, cooperatively monitor and retrospectively evaluate performance
Agencia de Evaluación de Tecnologias Sanitarias (AETS) (1) September 1997	• SRS requires highly qualified staff, therefore, concentration of care to a few specialized centres maintains quality • A continuous quality program of each one of the procedures (diagnostics, dosimetry, SRS) must be elaborated • There is insufficient information to compare the effectiveness of GK and LINAC treatment modalities • Evaluation of the results of radiosurgery is limited by several issues: poor quality of the evidence, incomplete description of patients treated, heterogeneity with regard to selection of cases, definition of successes or failures and duration of latency period from the time of treatment to the measurement of the result.

Technical Aspects

Details of the SRS procedure are described elsewhere (4,22,32,36,53,57). The term "radiosurgery" implies that the growth or malformation can be precisely targeted, eliminated, and is intended as a substitute to surgery (18). The successful endpoint of SRS for tumours is necrosis, or cell death, with as little damage as possible to surrounding tissue. In the case of AVMs the endpoint is obliteration (13,14,20,21,22,24,25,51).

SRS Procedure

In the usual pre-procedure preparation, a stereotactic head-frame is attached to the patient's head under local anesthetic. Magnetic resonance imaging (MRI), contrast-enhanced computerized tomography (CT) and/or angiography are performed to provide a three-dimensional plan of the location of the lesion or tumour. Once the coordinates are determined, a multidisciplinary team determines an optimum dose plan (26). Health care professionals involved should include a neurosurgeon, radiation oncologist, medical physicist, radiologist, neurologist, radiation therapist and nurse.

After planning is completed, the location of the isocentre, (the centre of the lesion) is verified. The patient is attached to the SRS device via the stereotactic head-frame and irradiation of the lesion begins. The treatment lasts approximately 40 minutes including the patient treatment setup (Mihailidis, personal communication). In fractionated radiosurgery, the patient has more than one treatment, which may be provided over 2 or more days depending on the total dose used. If this is the treatment regime chosen for the patient, a relocatable head-frame is used. This is not fastened to the skull -- instead the patient is fitted with a non-invasive removable frame, moldable thermoplastic mask or a bite block (4).

After SRS the patient's head-frame is removed. He/she is observed for a few minutes and then discharged from the clinic.

Side effects of SRS include swelling of the tissues being irradiated. This indication is usually treated by corticosteroids such as dexamethasone (Findlay, personal communication). Patient follow-up varies and is decided by physicians and specialists caring for the patient. At some centres, in the case of AVM, radiosurgery may be repeated if obliteration has not occurred after 3 years (22,51).

Imaging and Dosimetry

Dosimetry (dose prescription) for the patient is decided by the SRS team. One of the most important aspects of SRS dose planning is targeting. The diagnostic imaging procedures collectively permit localizing the target in three dimensional space. Claims by both the LINAC and GK manufacturers of ≤0.5 mm accuracy do not reflect overall accuracy in defining the target and refer to the isocentre localization. The accuracy achievable by diagnostic imaging is 1 mm for angiography and 1.5 - 2.0 mm in CT scan and MRI (4,9,46) so that the target for SRS

treatment is less accurately defined.. A high degree of expertise in imaging and planning is essential.

Characteristics of the GK and LINAC methods are outlined in Table 2. Some of the limitations may decrease with further developments in technology.

Table 2: Some characteristics of SRS methods

GAMMA KNIFE	LINAC
STRENGTHS:	**STRENGTHS:**
• accurate, reliable beam delivery	• accurate, reliable beam delivery
• no moving parts, ensures precision	• great flexibility in altering the pattern of beam delivery
• dedicated machine, therefore short set-up time	• acquisition cost is relatively low
LIMITATIONS:	• no field size limitation
• fractionated therapy is difficult at this time	• field shaping is relatively easy to achieve
• relatively high acquisition cost	• can be used for SRS body sites and conventional radiation therapy
• field sizes are limited, requires extensive use of multiple isocenters	• accurately delivered fractionated treatments are possible
• no realistic potential for individually shaped isocenter fields	**LIMITATIONS:**
• cobalt-60 source must be replaced every 5-10 years (a 1995 cost was $500,000 and took 10 calendar days (4))	• more extensive quality assurance procedures to guarantee safety and reliability compared to GK
	• system set-up is time consuming and labour-intensive

Sources: References (7,17,27,28,29,40)

Safety and Quality Issues

The premise behind SRS is that a focused beam enters the body and destroys the tumour or malformation while sparing normal tissue. To ensure that SRS is safe for use and that normal tissue is spared, many factors have to be addressed. As well, short- and long-term complication rates need to be determined.

The Radiation Therapy Oncology Group, which includes members from Canada and the U.S., is a multi-institutional cooperative organization whose principal objectives include: 1) increasing survival of patients with malignant diseases; 2) demonstrating the contributions of new modalities to the therapy of cancer; 3) improving the quality of life of patients who are not cured; 4) preventing second and subsequent malignant tumours among patients cured of cancer; and 5) seeking greater understanding of the biology of several types of cancer[1]. This cooperative developed quality assurance guidelines for radiosurgery (47). Their reasons were fourfold:

- to ensure that participating institutions have the proper equipment and appropriate techniques;

[1] Information extracted from the RTOG website: http://www.rtog.org/history/

- to outline a standard data set for each treated patient to assess protocol compliance;
- to define minor and major deviations in protocol treatment; and
- to set forth clinical data necessary to determine treatment efficacy including failure patterns and treatment toxicity.

Others have addressed issues of risk and consequences of SRS. The American Association of Neurosurgeons (AANS) and the American Society of Therapeutic Radiation Oncologists (ASTRO) held a conference and developed a consensus statement on SRS and Quality Improvement. The issues that were covered are summarized in Table 3 and include; patient selection, technical standards, gamma knife technology, linear accelerator technology, training guidelines and education.

Table 3: Summary of consensus statement on quality improvement in SRS

The American Association of Neurological Surgeons Task Force and the American Society of Therapeutic Radiation Oncologists Task Force decided the following by consensus:

Patient selection: SRS treats small, well-circumscribed, tumours or AVM readily identified by diagnostic imaging techniques. The selection of SRS over other treatment modalities involves an assessment of its risks and likely benefits in the context of patient preference, general anesthesia concerns, need for precise targeting during irradiation, and the radiobiological efficacy of alternative radiation techniques. Thus, patient selection requires a multidisciplinary team of neurological surgeons, radiation oncologists, medical physicists, nurses, diagnostic radiologists, and radiation technologists.

Technical standards: SRS systems must meet the technical standards for a strict program of quality improvement and assurance. These programs have been evaluated by the Nuclear Regulatory Commission for GK technology and the Food and Drug Administration for LINAC technology.

Gamma Knife technology: Centres must comply with the appropriate nuclear regulatory body and respond to their daily, weekly, monthly and/or yearly requirements for quality assurance.

Linear accelerator technology: Frequent verification of the exact spatial relationship between the coordinate localization system and the mechanical isocentre of the LINAC couch-gantry system is required before each treatment session.

Training guidelines: Attendance at specific courses or symposia along with a site visit, observation of patient planning and treatment at one or more centres currently performing SRS. Education should include analysis of previous results, patient selection guidelines, SRS head-frame application techniques, SRS neurodiagnostic imaging using all pertinent modalities, target selection, dose determination, dose prescription, treatment delivery and instructions regarding radiation effects, protection and recognition of complications.

Source: Reference (5)

In addition, all SRS units should possess the following emergency standards and safety facilities:

- Sufficient space for head-frame application
- Life support mechanisms to handle potential medical emergencies

- Neurodiagnostic imaging facilities to provide high resolution imaging
- Emergency safety and technical standards must be defined, posted and followed at each centre
- Redundant methods of measuring radiation output

LINAC systems should include the following safety features:

1) rotation toward non-collision positions whenever possible;
2) the use of interlocks that prohibit rotation into a collision position; and
3) the use of interlocks to prevent table motion in any direction during treatment (5).

Follow-up guidelines

Diligent post-treatment assessment of patients is critical both to the patient and the field of SRS. The consensus statement made the following points:

- Evaluations should be timed so as to optimize the chance of detecting both the complication of and the favourable responses to treatment
- Evaluations should be standardized and whenever possible be conducted by the treating physician
- Compilation and analysis of results should be shared with others performing SRS (5).

With respect to the certification requirements of the two types of treatment device, the United States Food and Drug Administration advises:

> That both the GK and the modified LINAC are used for stereotactic radiosurgery of the head. They are both cleared through the 510(k) process which means that they were found substantially equivalent to radiation therapy devices that were marketed prior to May 29, 1976. The focused LINAC and GK devices are approved with broad indications for use (e.g. for "radiation therapy"). They generally are not cleared for specific procedures. These two devices allow high dose treatment of lesions in the head. They do this by using multiple beams, all focused at a single point, or using one beam that follows arcs around the head, thus spreading the radiation exposure over a large area of skin. Any one area of skin receives a low exposure while the cumulative exposure at the focus is high (therapeutically useful). Both devices are primarily used to treat malignant and benign tumours, and arteriovenous malformations of the brain (Phillips, personal communication).

In general, there are several policies and procedures available that define the safety and quality issues of both GK and LINAC stereotactic radiosurgery.

Efficacy and Effectiveness of SRS

The main indications for SRS are treatment of AVM, acoustic neuroma and brain metastases. Other conditions for which SRS has been used alone, or as an adjunct to surgery, include

primary brain cancer, pituitary adenoma, meningioma, trigeminal neuralgia (see Appendix B), epilepsy and Parkinson's disease (4,35,42,48,55).

Tables 4, 5 and 6 summarize results from recent studies on SRS in treatment of AVM, acoustic neuroma and brain metastases. Comments on the quality of evidence presented refer to the classification published by Jovell and Navarro-Rubio (33). In that classification 'Good' refers to evidence from meta-analysis of randomised controlled trials (RCTs) or from large sample RCTs; 'Good to Fair' to that from small sample RCTs and non-randomised controlled prospective trials; 'Fair' to results from non-randomised controlled retrospective trials, cohort studies and case-control studies; and 'Poor' to information from non-controlled clinical series and various other approaches. Assignment to categories is also dependent on conditions of scientific rigour.

The results summarized in the tables are inconsistently reported. For example, outcome goals for brain metastases included increased survival, tumour shrinkage and/or tumour control. In the case of AVM, outcomes were measured by a decrease in seizures or obliteration of the malformation. Acoustic neuroma outcomes were reported as either complete, partial or no tumour response.

In general, there continues to be an absence of controlled studies, with most reports referring to case series, mostly considered retrospectively.

Treatment of brain metastasis

A number of reports on SRS treatment of brain metastasis make comparison with the results of two RCTs undertaken by Patchell et al. and Noordijk et al. (39,41). These compared the results of radiotherapy (RT) alone with radiotherapy plus surgery. Both studies provide good to fair evidence that combined radiotherapy and surgery gives better survival and functional independence than radiotherapy alone.

The results from these two RCTs are cited in a number of the reports on SRS of brain metastases to provide a comparison of treatments. The SRS studies do not, therefore, have controls but instead rely on data from small studies at different centres and with different populations. In general, only the overall findings of Noordijk et al. and Patchell et al. are considered and there is no attempt to assess the comparability of the study populations. Many of the SRS studies can therefore be classified as uncontrolled case series, giving a fair to poor level of evidence of outcomes.

Recent studies on SRS for brain metastasis are summarized in Table 4. The two "comparison" studies of RT versus RT plus surgery are also included.

Overall, the results suggest survival periods following SRS to be comparable to the "comparison" studies, with indications of improved functional independence and quality of life. There were high levels of local control (an intermediate measure) in a number of studies. It seems clear that substantially worse outcomes are obtained in patients who have more than two detectable metastases.

The study from the MD Anderson Cancer Center in Houston by Bindal et al. differs from the others in that it reported longer survival after surgery alone than after SRS (10). Commentary on this paper (54) suggests a bias in favor of surgery and limitations in the SRS procedure that was used. On the other hand, this is the only study that reported comparative data from the same institution. A review paper from the same centre concluded that surgery should remain the treatment of choice whenever possible (45).

On the basis of the literature reviewed, and the earlier assessments, the place of SRS in treatment of metastatic disease is still not established. It appears to have a place in the treatment of appropriately-selected patients with one or two metastases, and is a useful option when the patient is not a candidate for surgery. Further, better quality, studies are required.

Table 4: Outcomes of surgery versus SRS in the treatment of brain metastasis

Surgery *with* versus *without* RT

Study	Number of Patients (Lesions)	Treatment Modality	Outcomes	Comments
Patchell, et al. (41) Prospective RCT 1990	23 (23) 25 (25)	RT alone Surgery + RT	Median Survival: 15 wks QALY: 12 wks Median Survival: 40 wks QALY: 35 wks Of the patients who died, 71% in the surgical group and 50% in the radiation group died of systemic causes, i.e. surgical treatment of the brain metastasis was positively correlated with neurologic survival. Patients treated with surgery remained functionally independent longer (38 wks vs. 8 wks) than those in the radiation group.	Good to fair level of scientific evidence. Small sample size. No mention of lesion size. An important finding in this research was that 11% of patients did <u>not</u> have metastatic disease despite having findings on CT and MRI that were consistent with single brain metastases.
Noordijk, et al. (39) Prospective, Multi-centre RCT 1994	31 (31) 32 (32)	RT alone Surgery + RT	Median Survival: 6 mo QALY: 12 wks Median Survival: 10 mo QALY 35 wks Patients with active extracranial disease had the same median survival duration irrespective of given treatment. Conversely, those with inactive extracranial disease survived (12 mo) and remained functionally independent longer. Patients remained functionally independent until a few weeks before death.	Good to fair level of scientific evidence. Sample size is small. No mention of lesion size.
SRS outcomes				
Buatti, et al. Retrospective ('89-'93) (12) 1995	25(28) follow-up included imaging performed 3 months after SRS and every 6 months.	LINAC: 10-15 Gy Median 15 Gy 12 received SRS as initial treatment, 13 were treated at time of recurrence after WBRT.	Median Survival: 6.6 months post-SRS, 37 months from diagnosis. Local control rate was 84%, and was defined as no evidence of progression on follow-up scans. Progression was defined as more than a 25% increase in size. The variable of time to development of brain metastasis was the only significant predictor of outcome.	Fair level of evidence, small sample size, retrospective study. Median treatment volume 11.4 cm^3, corresponded to a lesion 2.8 cm in diameter. No mention of functional independence.

Table 4 (continued)

Auchter, et al. Multi-institutional, retrospective, ('89-'94) (6) 1996	122 (122) median follow-up 123 wks (range 7 to 314 wks)	LINAC: 10-27 Gy + RT (Median 17 Gy) Dose contingent on lesion size and location	Median Survival: 56 wks QALY: 51 wks Median duration of functional independence was 44 wks. The most significant predictor of survival and functional independence was KPS at the time of SRS; the better the KPS, the longer the median survival. Local control rate was 86%.	Fair to poor level of scientific evidence, retrospectively matched, "careful" selection criteria. Median tumour volume 2.68 cm^3.
Bindal, et al. (Retrospective '91-'94) (10) 1996	31 (7 >1 lesion) 62 (16 > 1 lesion) Follow-up neuro-imaging at 1,3,6,12 and 18 months until last examination or death	SRS: 12-22 Gy (22 + RT) Median 20 Gy, single isocentre only Surgery (41 + RT)	Median Survival: 7.5 months Median Survival: 16.4 months Difference in survival due to a higher rate of mortality from brain metastasis in the SRS group; there was greater progression of treated lesions and not the development of new brain metastasis. In the surgical group 53% of the deaths were from systemic disease.	Fair to poor level of scientific evidence, lesion locations not mentioned. Neurosurgery dates not mentioned. Method of WBRT not described. Comparative SRS results are from older series. Median tumour volume 1.96 cm^3.
Flickinger, et al. Retrospective study ('88-'95) (18) 1996	157 (229) 112 single tumour 33 had 2 tumours 7 had 3 tumours 3 had 4 tumours 2 had > 4 tumours Median follow-up was 8 months	GK: 12-25 Gy Median minimum dose 16 Gy, dose contingent on lesion size and location	Median Survival: 10 months observed for patients with solitary tumours; 7 months observed for multiple tumours. Tumour disappearance, tumour shrinkage, or stable tumour size was found in 86% of the treated patients. Recurrent tumours were treated in 20% of patients.	Fair level of scientific evidence. Patient evaluation criteria not defined. No statements on length of functional independence. Mean target volume was 3 cm^3.
Gerosa, et al. Retrospective study ('93-'95) (23) 1996	225 (343) a subset of 152 (236), no breakdown of number of lesions per patient Mean follow-up 53.1 wks (range 16-140)	GK: Mean dose 21.1 Gy, Average dose 30.2 Gy, contingent on lesion size and location.	Median Survival: 40 wks Fully eligible 51 wks, non-eligible 32.3 wks 1 year local tumour control rate was 88.2% Functional independence (□) 24 wks, fully eligible 36.5 wks, non-eligible 17.5 wks. Focal recurrence observed in 11.8% of patients.	Fair to poor level of scientific evidence. Control of primary tumour determined "eligibility" as well as ≤ 3 lesions, target volume of ≤ 20 mL, WBRT within 6 wks. There were 51 out of the 152 who were "eligible". Mean tumour volume 5.7 cm^3.

Table 4 (continued)

Joseph, et al. (Retrospective '89-'93) (32) 1996	120 (189) 70 single tumour 30 had 2 tumours 16 had 3 tumours 4 had 4 tumours (consecutive patients) Follow-up CT or MRI scans were generally obtained at 3-month intervals	LINAC: 10-35 Gy Median 26.6 Gy, dose contingent on lesion size and location 100 patients had WBRT: 54 before, 38 after and 8 concurrent with SRS. The other 20 patients refused WBRT.	Median Survival: 32 wks 37 wks observed for patients with one or two metastases, 14 weeks for patients with 3 or 4 metastases. Extracranial disease was either treatable or under reasonable control. Survival duration of SRS + RT are comparable to Patchell's (37) results of surgery + RT (37 wks v. 40 wks, respectively). The best survival rates were found in patients with ≤ 2 brain metastases.	Fair level of scientific evidence, retrospectively matched to data from separate study. No mention of functional independence. Mean target volume was 5.31 mL.
Breneman, et al. Retrospective study ('89-'95) (11) 1997	84 (177) Follow-up MRI requested at 3 month intervals, 11 patients had no follow-up imaging	LINAC: 10-22 Gy Median 16 Gy, dose contingent on lesion size and location. 79 patients received SRS after WBRT failed to stop progression of their brain metastases; 4 patients had SRS as a boost following RT	Median Survival: 43 wks from RS, 71 wks from diagnosis 1-2 lesions 44 wks > 2 lesions 35 wks Total complication rate of 11% (9/84) with 2% (2/84) requiring surgical decompression; both patients were found to have radiation necrosis. 38 patients (45%) had active extracranial disease.	Fair to poor level of scientific evidence. Eleven patients unavailable for follow-up; 73 were eligible for local control analysis. No mention of functional independence. Tumours were < 40mm in greatest dimension.
Shiau, et al. Retrospective study ('91-'94) (49) 1997	100 (219) 119 lesions were recurrent after EBRT. Lesions were followed by MRI and/or CT imaging every 3 months. Median clinical follow-up 80 wks (range 25-182).	GK: 10-22 Gy Median dose: 18.5 Gy 112 lesions had prior RT 55 lesions had RT + SRS boost 45 lesions had SRS alone 7 lesions had prior surgery + RT	Median Survival: 48 wks Successful endpoint described as lesion's "freedom from progression" (FFP). Actuarial FFP was 82% at 6 mo and 77% at 1 y for all lesions. For lesions receiving ≥ 18 Gy the actuarial FFP was 93% and 90% respectively. Complications were documented in 14 of 100 evaluable patients.	Fair to poor level of scientific evidence. Median tumour volume was 1.3 mL. Authors conclude a minimum prescribed SRS dose of ≥ 18 Gy yields excellent local control of brain metastases

SRS = Stereotactic Radiosurgery
LINAC = Focused Linear Accelerator
GK = Gamma knife
RT = Radiotherapy
RCT = Randomized Control Trial
KPS = Karnofsky Performance Status
WBRT = Whole Brain Radiotherapy

Treatment of AVMs

The seven studies summarized in Table 5 provide generally weak additional evidence to that considered in earlier assessments. SRS is useful in appropriately selected patients, but there appears a need for long-term follow-up, to include consideration of adverse effects.

Although the study by Yamamoto et al. was retrospective, it is one of the few long-term studies that looked at effects of SRS over time. They concluded that follow-up should continue even after treatment goals had been reached, because of delayed radiation effects (56).

There is no real indication of the proportion of AVMs that might appropriately be treated by SRS alone or in combination with embolization. In many cases, surgery will remain the preferred option.

Treatment of acoustic neuroma

Table 6 gives details of six studies of SRS in treatment of acoustic neuroma. There are indications of benefit through local control and acceptable longer-term outcomes, but with some concerns regarding possible complications. SRS appears to be a useful option for appropriately selected patients, but surgery will often be the preferred option.

A retrospective outcome study by Deen et al. used "observation alone" as a treatment strategy used because of patient preference, advanced age, minimal symptoms and/or poor general medical condition. Out of 68 patients observed, 58 were successfully managed and 10 patients eventually required treatment at a mean interval of 4 years after diagnosis. Deen et al. conclude that observation is a reasonable management strategy in carefully selected patients with acoustic neuroma. However, diligent follow-up is required to assess if active treatment is required (15).

Table 5: Outcomes in the treatment of arteriovenous malformations with GK versus LINAC

Authors	Number of Patients	Treatment Modality	Outcomes	Comments
Coffey, et al. Retrospective study ('90-'93) (14) 1995	121 53 prior hemorrhage 59 prior seizures 13 prior surgery 13 prior CVE 4 prior SRS Follow-up 6 - 55 mo	GK: 16-20 Gy , dose contingent on lesion size and location.	89 patients neurologically stable 22 experienced neurologic improvement 2 permanent deficit 1 temporary deficit 3 non-fatal hemorrhage 2 fatal re-bleeding 2 death from other causes	Poor level of scientific evidence. Sample size is good but obliteration outcomes are reported for a subset of patients. Authors conclude that SRS results are superior to the natural history of untreated AVMs and, in certain instances, are superior to the results of conventional surgical treatment. AVM size range: < 1 to > 10 cm^3
Yamamoto, et al. Retrospective, long-term follow-up study ('78-'91) (56) 1996	40 1 had prior clipping of the feeding artery 1 had prior CVE 1 had prior RT Follow-up was 54 to 205 months.	GK: 24-70 Gy mean dose: 42 Gy, dose contingent on lesion size and location.	26 angiographically proven obliteration (26/39), (1 patient refused follow-up procedures). 65% -corrected (follow-up was between 1 - 5 years) 13 patients showed shrinkage, incomplete nidus obliteration showed up on follow-up angiographs (follow-up was 3 - 7 years following SRS) 1 of the 13 had surgery, 5 of the 13 patients underwent a second round of GK SRS 3 of these 5 showed angiographically proven obliteration 3 patients who underwent CT and/or MRI > 5 years after SRS showed delayed cyst formation.	Poor level of scientific evidence. Patients followed over a 13 year period originally had SRS at different centres. AVM volumes ranged from 0.15 to 28.08 cm^3. SRS techniques would have changed over this time frame. Authors conclude that long-term follow-up, particularly with the use of neuro-imaging techniques, is necessary even after the treatment goal has been achieved.
Gerszten, et al. Retrospective study ('87-'94) (24) 1996	15 all presented with ≥ 1 seizure, 8 had prior hemorrhage, 3 prior partial resection, 7 prior embolization Follow-up: 12 to 83 months (□ 47 mo).	GK: 15-25 Gy mean dose: 20 Gy, dose contingent on lesion size and location.	Outcome goal: seizure free 11 patients seizure free 2 patients significant improvement 2 patients developed seizures	Poor level of scientific evidence. Small sample size. Outcome was not obliteration as in other series. Mean AVM volume: 3,693 mm^3

Table 5 (continued)

Zakhary, et al. (abstract only) Follow-up study (59) 1996	75	GK: (particulars of treatment not given in abstract) LINAC:	71% complete obliteration (after 19 months) GK - 20.7% incidence of hemorrhage, 11% neuro. deficit 76% complete obliteration (after 24 months) LINAC - 18.6% incidence of hemorrhage, 14% neuro. deficit	Abstract only. Study suggests that efficacy, long-term outcome and complications are comparable for treatment of AVMs with either the GK or LINAC.
Pica, et al. Retrospective follow-up study ('89-'92) (43) 1996	41 25 prior hemorrhage 6 previous surgery 16 CVE 1 CVE and surgery Follow-up 3-55 mo, median 34 mo.	LINAC: 15-20 Gy, dose contingent on lesion size and location.	26 angiographically confirmed complete obliterations 3 angiographically confirmed > 80% obliteration 3 angiographically confirmed < 80% obliteration 9 of the 41 patients were lost to follow-up 11 patients (27%) experienced treatment associated toxicity 8-24 mo after SRS; 4 recovered completely, 3 improved clinically but have pursued drug therapy and 4 experienced serious and irreversible neuro-dysfunction directly attributable to SRS.	Poor level of scientific evidence. Authors stated that complete obliteration was influenced by AVM size, those smaller than 30 mm in maximum diameter showed 85% obliteration. Mean estimated volumes of AVMs 1.4, 7, and 13.8 cm^3
Steinberg, et al. Retrospective study ('90-'94) (51) 1996	33 Surgery **after** SRS 45 operations in 33 patients. Clinical follow-up (12-84 months)	Multi-modality AVM program included: surgery proton beam, gamma knife and/or linac: 4.6-45 Gy and/or embolization	28 angiographically confirmed complete surgical resection (85%) 5 patients had planned partial resection (due to size of AVM) 21 patients - excellent; 10 patients - good; and 2 patients dying secondary to hemorrhage from residual AVM Clinically speaking, 4 months after surgery 22 patients were neurologically unchanged, 6 were better and 5 were worse.	Poor level of scientific evidence. Small sample size. Authors state that prior SRS decreased the surgical morbidity and improved the clinical outcome compared with preoperative embolization alone. AVM sizes ranged from 1 to > 5 cm
Young, et al. (57) 1997	50 26 prior hemorrhage 18 prior seizures 4 prior headache 3 - 6y 8mo follow-up	LINAC: 12-25 Gy mean of 21.2 Gy, dose contingent on lesion size and location. 17 had prior CVE 3 had prior surgery 6 had prior surgery+CVE	25 (50%) angiographically confirmed obliteration 2 AVM obliterated but residual dural component (also successful) (50%+4%=54%) 4 presumed cured (MRI only) 13 partial response at 3 years 1 required surgery, 1 fatal hemorrhage 1 no response and 3 no two year follow-up	Fair to poor level of scientific evidence. All outcomes reported were after a minimum of 2 - 3 years follow-up. Authors recognize the flaw in other series that report on subsets of patients, recommend standard methods of describing results.

Table 6: SRS in the treatment of acoustic neuroma (vestibular schwannoma)

Authors	Number of Patients	Treatment Modality	Outcomes	Comments
Pollock, et al. Retrospective study ('90-'91) (44) 1995	87 Follow-up: patients in both treatment groups were contacted a minimum of 2 years after surgery.	Surgery: 40 GK SRS: 47 25-36 Gy contingent upon tumour size and location	Long term results: 31 (78%) patients had Facial Grade* I or II Return to Functional Independence: < 1 month = 12 (30%) ≤ 6 months = 21 (53%) Long term results: 43 (92%) patients had Facial Grade I or II Return to Functional Independence: < 1 month = 35 (75%) ≤ 6 months = 6 (13%)	Fair to poor level of scientific evidence. "Careful" selection criteria. Outcomes are "facial nerve function (patient's perspective of therapeutic success)" "useful hearing", and "functional independence". As well, there is a "patient's subjective rating of tumour management". Authors question whether hearing preservation should be a goal of acoustic neuroma surgery. Avg AN < 3 cm in size
Hirato, et al. (30) 1995	28 3 patients bilateral tumour 6 already deaf when treated Mean follow-up was 16 mo, longest 24 mo.	GK SRS: 25.2 Gy (□) at the centre	69% had lowering of the MRI signal intensity in tumour centre 59% had tumour shrinkage 3 cases of enlarged tumour 2 cases of hydrocephalus Hearing preservation (22 patients evaluated):85% at 3 mo 80% at 6 mo 75% at 12 mo 60% at 18 mo 50% at 24 mo	Abstract only Authors conclude that low dose GK SRS is effective in suppressing growth of acoustic schwannoma with preservation of hearing. Maximum tumour diameter was 35 mm.
Mendenhall, et al. Retrospective study ('88-'94) (38) 1996	56 Follow-up: minimum of 1 year	LINAC SRS: 10-22.5 Gy, contingent on lesion size and location.	55 patients (98%) achieved local control 13 patients (23%) developed complications 5-year actuarial local control rate was 95% Risk of complication was related to the dose and treatment volume	Abstract only "Local control" is the endpoint defined, therefore, LINAC SRS results cannot be compared to surgical outcomes. Tumour sizes not mentioned.

Table 6 (continued)

Forster, et al. Clinical series ('86-'89) (19) 1996	27 (29) in 2 series Follow-up: median of 6 y 7 mo,	GK SRS: 25 Gy to periphery (Group 1, 15 patients) 17.5 Gy to periphery (Group 2, 12 patients)	Success endpoint was control of tumour size or shrinkage lack of growth = tumour control 10% decrease in tumour diameter = shrinkage Group 1: tumour control in 12/17 tumours, failure in 5. Group 2: tumour control in 11/12 tumours, failure in 1. Group 1 patients had higher incidence of cranial neuropathy; complete facial palsy in 1 patient, partial weakness in 2 patients and transient in 2 patients. Trigeminal neuropathy developed in 4/14 patients with normal facial sensation. Group 2 showed 1/9 patients had partial loss of facial nerve function and 1/11 patients had transient facial sensory loss. Preservation of useful hearing in 4/11 patients in Group 1 and 5/7 patients in Group 2.	Poor level of scientific evidence. Good patient follow-up. Authors conclude that SRS is an effective alternative treatment for patients with tumours < 3 cm in diameter with negligible mortality and morbidity compared with surgery. Advantages are short hospitalization and maintenance of functional level and employment status after the procedure. However, SRS does not replace microsurgery but should be considered as an alternative. Tumour ≤ 3cm.
Varlotto, et al. Clinical series (52) 1996	12 4 patients prior surgery Follow-up: 16-44 mo, median of 26.5 mo	LINAC SRS: Fractionated regime - 54 Gy total dose in 27-30 fractions of 1.8 Gy/day.	Endpoint: tumour regression/stabilization. After a median follow-up of 26.5 mo, local control was found in 12 out of 12 lesions; 3 showed tumour regression, the remaining 9 tumour stabilization. One patient developed worsening of pre-existing 5th cranial neuropathy, 1 experienced a decrease in hearing.	Abstract only. Authors concluded that SRS provided excellent local control without new cranial nerve deficits. Results, however, are tentative in nature because of small sample size and short median follow-up.

Table 6 (continued)

Ito, et al., Retrospective study ('90-'94) (31) 1996	46 consecutive patients Follow-up: >3 mo	GK: number of Gy not mentioned in abstract	Endpoints: pure tone audiometry, auditory brain stem response and caloric test. Tumour growth occurred in 2 patients; 7 of 38 patients with preserved hearing of any extent became deaf within 1 y with deterioration rate of 8dB/y. Preserved caloric response was present in 13 patients before treatment and disappeared in 9 patients 4-13 mo after treatment, however their hearing was preserved. Delayed facial palsy and persistent trigeminal neuropathy occurred in 10 and 7 of the 46 patients respectively. Severe facial palsy tended to persist.	Abstract only. Authors conclude that because of the serious facial nerve complications that occurred in some patients, further study to disclose the risk factors for neurological dysfunction would be needed for SRS to become a true, safe alternative to microsurgery.

AN = Acoustic neuroma (also known as vestibular schwannoma)

* Facial grade based on the scale of House JW, Brackmann DE: Facial nerve grading system. Otolaryngol Head Nec Surg 93:146-147, 1985.

Current options and requirements for SRS in Alberta

There is only limited information on possible SRS caseload in Alberta. The top three indications for SRS treatment are AVM, acoustic neuroma and brain metastasis. There are an estimated 20-30 new cases of AVMs per year (Findlay, personal communication). Acoustic neuromas also have an incidence of 20-30 new cases per year (Broad, personal communication). Only a proportion of patients with AVMs or acoustic neuroma would be candidates for SRS.

Metastatic brain cancers are not statistically tracked in Alberta. The median survival time for patients with untreated brain metastases has been reported to be as little as one month (6,16,32,41,49).

The National Cancer Institute of Canada states that an estimated 9800 new cases of cancer were diagnosed in Alberta in 1997[2]. In the literature it is reported that 10% to 30% of cancer patients will develop brain metastases (18,41). In Alberta this would translate to approximately 1,000 to 3,000 patients with metastatic brain disease. Only 5% of all patients with brain metastases would benefit from surgery; eligibility for surgery included one metastasis that was surgically accessible (Urtasun, personal communication).

Of these cases, perhaps 50% are candidates for SRS (Urtasun, personal communication). The initial caseload for the Province might be 30 to 50 patients per year. Opinion from several specialists in Alberta is that SRS-treated cases would increase should a facility become available here.

Currently the treatment of choice for Alberta patients is surgery or microsurgery in combination with EBRT for metastasis in the brain. When the tumour or malformation is inoperable, procedures such as SRS are considered. In the last year there have been four patients who went outside the country for GK SRS. Most Alberta patients are sent to Ontario (Bayview/Sunnybrook) for LINAC SRS. Costs of the procedure and of travel (with a companion) are covered by Alberta Health Care. The time between a referral and treatment is a minimum of two months (Findlay, personal communication). LINAC SRS facilities are also available in Quebec and British Columbia.

[2] Information obtained from the National Cancer Institute of Canada website: http://www.cancer.ca/stats/

Cost-related considerations

Out-of-province referral

The price of SRS treatment to the Alberta health system under current arrangements depends on the location of the SRS site to which the patient is referred.

Sending patients to the U.S. for Gamma Knife® SRS treatment

The charge per Gamma Knife® procedure in the U.S. is estimated at $28,000 to $30,000 per patient. This includes treatment costs (hospital and physician services) and depreciation. In addition, there would be travel and accommodation costs (approximately $1,700 for two persons). In total, then, SRS, obtained in the U.S., would cost the Province about $30,000.

Sending patients to other provinces for focused linear accelerator SRS

An actual cost that Alberta Health paid the province of Ontario was $3,022 plus $5,100 physician costs for a patient who had LINAC SRS treatment. This case involved a hospital stay, which would not always be required. Physician costs could, therefore, be lower for many patients. In addition, there would be travel and accommodation costs, which would be about $3,000 for two persons. Total costs could be of the order of $8,000 to $11,000. Potentially, costs could drop somewhat if the facility in Vancouver was able to accept patients from Alberta.

As there is no evidence of any difference between the GK and LINAC methods in terms of effectiveness, there seems no justification for referring patients to the USA for GK treatment, in view of the substantial difference in costs to the Alberta health care system. Referral to centres in other provinces should be the preferred option, where SRS is indicated.

SRS within Alberta

A further option would be to develop SRS services within the province. The GK approach would be prohibitively expensive, given the high capital cost (of the order of $3.5M), need to replace cobalt-60 sources every five years (about $0.5M), building modifications, the single-purpose nature of this apparatus and the small caseload in Alberta. Therefore, only the option of developing a LINAC-based facility is considered in detail. The LINAC approach offers the cost advantage of using existing radiotherapy equipment with relatively modest additional expenditure.

In the following analysis it is assumed that:

- patient caseload would be 30 per year
- diagnostic work-up would be similar for either LINAC SRS or surgery
- follow-up services would show a similar utilization rate for both SRS and surgery
- endpoints are increased survival and quality of life for SRS and surgery.

With SRS the patient usually has one treatment. When two or more treatments are required, as in the case of fractionated therapy, the patient will receive the other treatments on subsequent days. On a single SRS treatment, from the time of admission to the conclusion of treatment, a total of 10 to 12 hours is required. There is no overnight hospital stay.

Patient flow would include:

- initial diagnosis, typically by a neurosurgeon: CT scan, angiography, MRI
- referral by neurosurgeon to the cancer clinic for SRS
- scheduling patient for treatment at the clinic following consultation with radiation oncologist
- application of SRS head-frame under local anesthetic (or attachment of relocatable head-frame)
- CT and/or MRI scan for treatment planning and to verify positioning of frame
- finalizing treatment plan by the multidisciplinary team (Table 7)
- preparation of linear accelerator for SRS (about one hour including set-up time)
- patient recovery
- discharge home

Costs of SRS are separated into capital equipment and ongoing operating costs. A true "cost" for a procedure must take into account all related staff and resources. Several factors must be taken into consideration: staff/institution costs, capital equipment or upgrade, and depreciation.

An estimated average cost for a hypothetical LINAC SRS procedure in Alberta would be based on the time commitments shown in Table 7. When average salaries are applied to these times, the average cost per procedure is $980.

The medical physicist has the largest time commitment (6 to 12 hours) followed by the radiation oncologist, nurse and radiation therapist. One of the neurosurgeon's roles is to attach the head-frame that is inserted with pins into the skull using local anesthetic. If a relocatable head-frame is used, these particular neurosurgeon services would not be necessary. However, as the neurosurgeon is an important part of the SRS multidisciplinary team his/her presence would still be required and a longer time commitment might be necessary than shown in Table 7.

Table 7: SRS team time commitments

Staff:	**hours:**
medical physicist	6-12
radiation oncologist	4-6
neurosurgeon	0.75
radiation therapist	1
nurse	2
Average estimated staff cost per procedure	**$980**

Linear accelerators are available in both Calgary and Edmonton as an integral part of radiotherapy services. About 40 patients per day per machine are treated (Cross Cancer Institute, personal communication). LINAC SRS can be offered with an upgrade to existing linear accelerators. Costs for an upgrade to permit SRS range from $200,000 to $500,000. The variation in upgrade costs are due to differences in the accoutrements that are available, (such as multi-leaf collimators, relocatable head-frame, couch or floor stand, commercial software) with upgrade packages. Typically, the linear accelerator is temporarily modified at the end of the day to deliver SRS.
In order to ascertain depreciation costs, the life of the equipment must be determined. The effective life of the equipment may be dependent upon technological advances more than equipment failure. If the upgrade costs for the linear accelerator are taken to be $350,000 (a mid-range value), and the "life" of the upgrade is 4 years, the annual cost for that equipment upgrade is $87,500. If there are to be 30 Alberta

patients treated per year then the price of the equipment per procedure would be $3000 ($87,500 ÷ 30). (Contribution of the depreciation of the basic LINAC equipment to SRS costs should be low and is ignored here.)

Based on these data, a rough per-patient cost in Alberta for LINAC SRS, including operating and medical costs, and the equipment depreciation would be $4000 per patient. There would, in addition, be minor travel costs within the province.

Although not included in this cost analysis, there is a significant start up commissioning overhead to any new radiation therapy program, including SRS. Such activities would include testing of the equipment, collection of radiation beam data, and enter this information in the treatment planning systems (Sandison, personal communication).

Costs of surgery

Surgery is the standard treatment for many patients with single brain metastasis, AVMs and acoustic neuroma. Table 8 gives examples of several related hospital costs for surgery. The estimated physician cost in Alberta for a surgical procedure is $2,266 for micro-brain surgery (Alberta Physician Fee Schedule, Alberta Medical Association) and $7,200 for hospitalization for an uncomplicated craniotomy (Jacobs, Hall, Bachynsky, An Alberta Standard Cost List, 1996), for a total of $9,466.

Table 8: Examples of hospital costs

Procedure	Cost per case
Craniotomy	$ 7,200
Neoplasm of nervous system	$ 3,600
Major head/neck procedure	$10,300

*From "An Alberta Standard Cost List for Heath Economics Evaluations", P. Jacobs, E.M. Hall and J. Bachynsky, v.1, March '96.

Comparison of costs

The indicative costs and charges given here indicate that LINAC SRS in Alberta might be a worthwhile option. At a cost per patient of about $4,000, an Alberta-based facility would compare favourably with referral to other provinces for SRS and be considerably cheaper than referral to the US for treatment with a GK (Table 9).

The comparison with surgery is less certain. SRS might well provide substantial cost advantages in appropriately selected patients. However, account would need to be taken of the cost implications of complications and the need for follow-up procedures, which might in some cases include surgery.

An underlying assumption is that an Alberta-based facility would operate with excellent quality assurance and have sufficient caseload for expertise to be developed or maintained. Given the expected caseload, only one SRS centre in Alberta would be realistic. Appropriate facilities and expertise are available at both Calgary and Edmonton.

Table 9: Summary of SRS and surgery costs

Treatment modality	Cost
LINAC SRS Alberta	$ 4,000
LINAC SRS Ontario	$ 8,000 - $11,000
Microsurgery	$ 9,500
GK SRS United States	$29,500

Patients who have acoustic neuromas, AVMs, or brain metastases all require certain diagnostic imaging procedures as well as supplemental procedures such as radiotherapy and/or chemotherapy. For information purposes these costs are outlined in Table 10. They are not considered in the cost analysis as they will apply to all treatment options. The costs shown include all physicians' costs, direct labour, materials, departmental overhead, and organizational allocated overheads.

Table 10: Diagnostic work-up and supplemental costs

Procedure	Cost
Radiation therapy	$2,900
Chemotherapy	$1,600
Angiography	$1,054
Magnetic Resonance Imaging	$ 677
Computed Tomography (CT enhanced)	$ 133

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.

The caseload for SRS in Alberta is uncertain, but might be 30 to 50 cases per year, on current indications. Given this caseload, the need for expertise and the wish for cost-efficiency, only one SRS site in Alberta would be appropriate, should a decision be made to introduce the technology.

The cost per case for an Alberta SRS facility might be of the order of $4,000. This would compare favourably with costs of out-of-province referral, either to centres in Canada or in the US. For some cases, SRS would provide a cheaper option than surgery, at least in the short-term. However, there would be a need to consider patient selection and longer-term outcomes very carefully before a judgment could be made on the appropriate place of each technology. An Alberta-based SRS centre should systematically collect data on the patients it treats, including long-term follow-up, and seek to develop links with other SRS centres in North America.

Appendix A : Methodology

A literature search was performed on MedLine, CancerLit, EMBASE, HealthSTAR, and Current Contents. The MeSH terms used were: radiosurgery/stereotactic radiosurgery/gamma knife/modified or focused linear accelerator/LINAC/costs/cost analyses/procedure costs/head and neck neoplasms. These terms were used alone or in combination. The search was limited to; human subjects, and years 1995-1997. A search of gray literature was also performed which included study of references cited on captured journal articles, stereotactic radiosurgery meeting proceedings and unpublished data.

Studies selected for further appraisal included all with patient numbers greater than 20. Given the known limitations of the literature, no restriction was placed on study design.

The Ontario Medical Association provided information regarding professional fees charged when an Alberta patient is treated in that province.

Alberta Health provided administrative data regarding patients who had received GK SRS in the USA and information on treatment charges for both LINAC and GK procedures.

Appendix B : Treatment of trigeminal neuralgia

During the preparation of this report, information about the effectiveness of GK SRS for the treatment of trigeminal neuralgia (TN) was urgently requested. The data that were gathered in response are summarized here.

A review of the recent literature revealed only four current papers specific to TN and they are outlined in Table 11. One of the driving forces behind the invention of the Gamma Knife® was the need for treatment of painful disorders such as trigeminal neuralgia (3,34,58). As such, GK SRS has been used for many years in the treatment of this disease. When medication cannot control the TN pain, then other treatments are considered. The following table is a sampling of outcomes in the treatment of TN using GK SRS and surgery as treatment modalities. Surgical procedures appear to have the best outcomes.

Table 11: Comparison of two treatment options for trigeminal neuralgia

Study	Treatment Intervention	Outcome
Kondziolka, et al. Multi-institutional study (34) 1996	**Gamma Knife** (n=50 patients, with 32 having had prior surgery)	At 2 years follow-up: 54% excellent control (pain-free, *most* patients able to discontinue medication) 34% had good control (50%-90% pain-free, patients continued medications) 12% treatment failure Authors conclude that the long-term results after radiosurgery remain to be identified.
Young, et al. Single institution study (58) 1997	**Gamma Knife** (n=60 patients, including 9 with tumour-related TN)	Follow-up was 6 months to 3 years Out of 51 patients (those without tumour): 58.8% excellent control (free of pain, and took no medications) 19.6% good control (pain decreased by 50% or more, small doses of medication required) 21.6% treatment failure (pain relief < 50%, and/or pain medication remained at pre-treatment levels) Authors state that only prolonged follow-up will identify the long-term recurrence rate with radiosurgical treatment. Only once long-term follow-up outcomes are known can radiosurgery be advocated as a primary treatment for TN.
Barker, et al. Long-term (20 year) outcome study (8) 1996	**Surgery** (microvascular decompression) n=1185	1155 patients followed for 1 year or more with a median follow-up of 6.2 years. Ten years after surgery: 70% excellent final results (pain-free without medication for TN) 4% occasional pain, no long-term medication Ten years after surgery, annual rate of recurrence of TN was < 1%. Major complications included: 0.2% mortality, 0.1% brain-stem infarction, 1% had ipsilateral hearing loss.
Slettebo, et al. Prospective study (50) 1997	**Surgery** (microvascular decompression) n=25	After a median observation time of 38 months: 80% (20 patients) pain-free 4% (1 patient) reported 50% pain relief No serious complications occurred. Minor dyaesthesias were reported by 8% (2 patients). A vascular compression of the trigeminal root was found intra-operatively in 23 patients.

The modern advances in microsurgery and modified LINAC have broadened the treatment options for this condition. In the literature it is stated that when medications such as carbamazepine, baclofen or phenytoin are ineffective then microsurgery, specifically microvascular decompression, is preferred over SRS (8,34). However, SRS is an acceptable option sometimes offered to those who are not candidates for surgery. Professional opinion states that if SRS is used, then either the GK or the LINAC perform equally well (Podgorsak, personal communication).

Appendix C : Glossary of Terms

AN	**A**coustic **N**euroma: a benign tumour of the 8th cranial nerve [acoustic region].
AVM	**A**rterio**v**enous **M**alformation: A malformation in arteries or veins. They consist of variable sized masses of twisted blood vessels.
CT	**C**omputerized **T**omography:: x-ray images from a computerized analysis of the differences in absorption.
EBRT (also WBRT and XRT, RT)	**E**xternal **B**eam **R**adiation **T**herapy: use of a radiation source (linear accelerator) for treatment of tumours.
GK	**G**amma **K**nife®: A stereotactic radiosurgery device that uses Cobalt-60 to deliver a high dose of radiation to the brain.
LINAC	**Lin**ear **Ac**celerator: A radiation therapy device that uses x-rays as a radiation source.
Meningioma	Slow growing tumour that originates in the arachnoidal tissue.
Metastasis	Cancer cells that have broken away from a primary tumour and result in secondary growth in a new location within the body.
MRI	**M**agnetic **R**esonance **I**maging: a type of imaging where the patient is subjected to a strong magnetic field.
Pituitary adenoma	A tumour in the pituitary gland.
Radiosurgery	A type of radiotherapy that focuses a precise beam of higher-dose radiation (either gamma or x- rays) focused on a tumour or malformation.
RCT	**R**andomized **c**ontrolled **t**rial, participants are randomly allocated by a process equivalent to the flip of a coin to either one intervention (such as a drug) or another (such as placebo treatment or a different drug).
Trigeminal neuralgia (TN)	A severe, sharp pain along the course of a nerve, tender points and or violent spasm of muscles, involving the gasserian ganglion of one or more branches of the trigeminal nerve.

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