Guideline Resource Unit
guru@ahs.ca

Stereotactic Radiosurgery: Arteriovenous Malformations, Pain and Movement Disorders, and Temporal Lobe Epilepsy

Effective Date: April, 2018

Alberta Health Services
CancerControl Alberta

Clinical Practice Guideline CNS-013b – Version 1
www.ahs.ca/guru

Background

Stereotactic radiosurgery (SRS) is a radiation technique that uses stereotaxis, multiple vantage points, and imaging technology to converge a high dose of radiation on a precisely defined target volume while minimizing irradiation to surrounding tissue.[1] Stereotactic irradiation can be delivered in a single dose as SRS or in multiple doses as fractionated stereotactic radiosurgery (FSRT), using either a Gamma Knife (GK) or modified linear accelerator (LINAC) treatment system.

The Gamma Knife was originally developed by Swedish physician Lars Leksell in 1951.[2] This form of SRS uses an array of 201 static colbalt-60 sources surrounded by an 18,000kg shield to converge a focused beam (isocenter) on a single target area. During treatment, the patient is immobilized using a stereotactic frame.[3] In contrast, a LINAC-based system uses a single radiation source rotated through multiple noncoplanar arcs to converge on the target lesion.[3] Both systems achieve a target accuracy of 0.1 to 1mm.[4] There are no clinical trials that compare Gamma Knife radiosurgery (GKRS) with LINAC-based radiosurgery. A rapid response report from the Canadian Agency for Drugs and Technologies in Health in 2014 was unable to distinguish between GK and LINAC-based SRS systems with regard to clinical effectiveness, safety and cost effectiveness.[5] In addition, RTOG 9508, a multicenter clinical trial that combined SRS with whole brain radiation therapy (WBRT) for the treatment of brain metastases, found no differences in efficacy or toxicity in patients treated with GKRS or LINAC-based SRS in subgroup analysis.[6] Therefore, the subsequent recommendations in this guideline will apply to both delivery methods.

SRS typically refers to the delivery of a high dose of radiation in a single session or fraction. Fractionated stereotactic radiotherapy, also known as FSRT, may be performed to reduce the dose to adjacent critical brain or spine structures and to provide greater dose homogeneity to the target tissue. In such cases, irradiation is delivered over multiple sessions or fractions, typically at a low dose.[7] This SRS guideline will include dose recommendations for FSRT as well as single-fraction SRS. While LINAC has typically been the modality used for FSRT, newer GK models also allow for treatment to be administered over multiple sessions.

Guideline Questions

1. What are the functional indications for SRS?
2. What are the dose recommendations for SRS?

Search Strategy

PubMed and EMBASE was searched at different time points between July 12, 2017 and November 11, 2017, depending on the subtheme. Medical Subject Headings (MeSH) included: intracranial arteriovenous malformations, trigeminal neuralgia, epilepsy temporal lobe, movement disorders, and radiosurgery. Across all subthemes results were limited to human participants over the age of 19 years, and studies published in English. Additional exclusion criteria depended on the subtheme. For

example, arteriovenous malformation studies that failed to report on obliteration rates, or risk of delayed hemorrhage were excluded.

The National Guideline Clearinghouse (HGC, Agency for Healthcare Research and Quality https://www.guideline.gov/) was searched for clinical practice guidelines related to the subthemes in addition to the webpages of other well recognized clinical practice guideline developers (e.g. Cancer Care Ontario, American Society for Radiation Oncology, and National Comprehensive Cancer Network).

Target Population

The recommendations outlined in the guideline apply to patients age 18 years or older. Different principles may apply to pediatric patients. A wide range of factors must be taken into account in assessing if SRS is the appropriate course of treatment for the patient. Functional disorders that can be treated by SRS include brain arteriovenous malformations (AVM), trigeminal neuralgia, temporal lobe epilepsy, and movement disorders.

Recommendations

General Principles:

1. Participation in clinical trials should be encouraged.
2. All new patients should be discussed in a multidisciplinary team meeting before treatment.
3. All patients considering SRS should have a clear understanding of its advantages, disadvantages, and limitations.

Brain Arteriovenous Malformations

4. The selection of patients suitable for SRS depends on prior bleeding history, age, comorbidities, anatomic location, and clinical history.
5. Single-fraction SRS is recommended for patients with small, surgically challenging AVMs (volumes <10 cm^3 or maximum diameter <3 cm).
6. Embolization before SRS is controversial, and is not recommended in newly referred patients. If embolization is clinically indicated in newly referred patients, it is recommended to be deferred until after SRS is delivered.
7. Large AVMs may be treated with either volume-staged or fractionated SRS, or, in pediatric and young adult patients, referred for consideration of proton beam therapy.
8. Patients may be treated with corticosteroid (e.g. dexamethasone, methylprednisone) on the day of the SRS procedure and can continue to take other medications (e.g. antiepileptics, analgesics) during and after the procedure.
9. After SRS, serial clinical exams and MRI are recommended annually for the first 2-4 years to assess the effect of SRS on neurologic function and the AVM volume. After this period, a follow-up conventional angiogram should be requested for confirmation. If obliteration is not confirmed

on a conventional angiogram after 2 years, a repeat MRI and conventional angiogram could be performed after one additional year.

10. Patients who have residual AVMs identified by angiography at 3 years (after SRS) may be candidates for a second (salvage) SRS procedure.

    Recommended dose prescription:

    - A marginal dose of 18 to 24 Gy.
    - Dose may be reduced to 16Gy for lesions in or near the brainstem.

Trigeminal Neuralgia

11. SRS is recommended for patients who are medically or surgically refractory, have comorbidities precluding invasive surgery or who have declined surgery.
12. The role of repeat SRS for TN requires further investigation but may be considered for salvage.

    Recommended dose prescription:

    - A single maximum dose of 70 to 90 Gy at the mid-cisternal segment of the TN nerve. Care should be taken to limit dose received by the brainstem.

Mesial Temporal Lobe Epilepsy

13. SRS is a treatment option for patients with a purely mesial location of the epileptogenic zone, and who are medically or surgically refractory, refuse resection, or who have medical comorbidities that increase perioperative risk.

    Recommended dose prescription:

    - A marginal dose of 20-24 Gy.

Movement Disorders

14. SRS pallidotomy in Parkinson's disease (PD) is not recommended because of the relatively high complication rate arising from the anatomical position of the globus pallidum.
15. SRS thalamotomy for treatment of intractable tremor is an option for patients who are considered high-risk for conventional surgery (e.g. those receiving anticoagulant therapy, the aged, or patients with systemic complications).

    Recommended dose prescription:

    - A single maximum dose of 130 to 140 Gy to the ventral intermediate nucleus (Vim) of the thalamus.

Other

SRS can be considered for other functional indications not covered in this guideline, such as hypothalamic hamartomas, obsessive compulsive disorders, and major depressive disorder.

Discussion

Brain Arteriovenous Malformations

Brain AVMs are tightly packed masses of dilated arteries and veins that are directly connected without an intervening capillary bed. While headaches, seizures, and neurologic deficits are common symptoms of AVMs, most are asymptomatic until they rupture and cause morbidity. AVMs occur in less than 1% of the general population.[8] The hemorrhage rate for unruptured AVMs is 2.2% and 4.5% for ruptured AVMs.[9] Risk factors for hemorrhage include prior hemorrhage, deep AVM location, exclusively deep venous drainage, and associated aneurysms. The cause of AVMs are unknown, but are believed to be congenital. AVMs are typically diagnosed before the age of 40 years. The Spetzler-Martin (SM) grading system can be used to stratify AVMs into low- (Grades I-II), intermediate (Grade III), and high-grade malformations (Grade IV-V), which are graded on the basis of size, pattern of venous drainage, and neurological eloquence of adjacent brain.[10] Grade I malformations are small, superficial, and located in non-eloquent areas; Grade V malformations are large, deep, and situated in neurologically critical areas; and Grade VI malformations are essentially inoperable AVMs.

Treatment options. Treatment decisions for AVMs are made by weighing the risks of leaving the vascular malformation intact against the risks of intervention.[11] The expertise of a multidisciplinary team is required to determine if SRS is the optimal for any given patient.[12] In patients in whom the risk of hemorrhage warrants intervention, treatment options include microsurgery, embolization, SRS, or a combination of these treatments. Van Beijnum et al. conducted a systematic review of 137 observational studies that reported on at least 15 consecutive patients of any age who underwent AVM treatment (13,698 patients and 46,314 patient-years of follow-up).[13] The authors reported that while case fatality after treatment decreased over time, treatment of AVMs was associated with considerable risks and incomplete efficacy. Case fatality was 1.1 after microsurgery, 0.50 after SRS, and 0.96 after embolization. Intracranial hemorrhage rates were 1.4 per 100 person-years overall, 0.18 after microsurgery, 1.7 after SRS, and 1.7 after embolization.

SRS. The primary goal of SRS is AVM obliteration without adverse radiation effects. Successful obliteration after SRS depends on the amount of radiation delivered and accurate identification of the AVM shunt. Complete obliteration rates vary between 50% and 90% depending on the AVM volume.[14] The primary risk to a patient after SRS for an AVM is the latency period to obliteration during which the malformation remains at risk for hemorrhage. Maruyama et al conducted a large retrospective observational study on the risk of hemorrhage after SRS for patients with AVMs (N=500).[15] As compared with the period between diagnosis and SRS, the risk of hemorrhage decreased by 54% during the latency period and by 88% after obliteration. The reduction was greater among patients who presented with hemorrhage than among those without hemorrhage at presentation. Based on a large number of single-center, retrospective cohort studies, single-session SRS is recommended as a safe and efficacious treatment option for patients with small AVMs, especially when located in deep or eloquent areas.[16,17] SRS is also recommended for patients who

are considered poor surgical candidates because of advanced age or comorbidities, and for patients who don't want invasive surgery.

SRS for unruptured AVMs. The only randomized controlled trial (RCT) to study the treatment of AVMs was stopped prematurely.[18] A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) aimed to compare the risk of death and symptomatic stroke in patients with an unruptured AVM who were allocated to either medical management alone (symptomatic treatment with medications, as needed; N=109) or medical management with interventional therapy (surgery, embolization or SRS; N=114). At the second planned interim analysis, efficacy of medical management for the prevention of death or stroke (observed log-rank Z statistic of 4.10) was shown to exceed the stopping boundary value of 2.87. The ARUBA trial has been criticized for its short follow-up period (mean 33.3 months) and disproportionate number of patients treated with surgery and embolization.[19] Several retrospective studies published after ARUBA have assessed outcomes after SRS for ARUBA-eligible patients and reported lower overall risk of stroke or death in the treatment arm than the 30.7% reported in ARUBA.[19-21]

SRS for large AVMs. Within most series, obliteration rates for large AVMs are reported less than for small AVMs.[22] An obliteration rate of 36% was reported in a multicenter cohort of 233 SM Grade IV-V AVMs treated by single session SRS.[23] The authors identified three predictors of successful obliteration: absence of deep location (p=0.044), no pre-SRS embolization (p=0.046), and absence of large AVM diameter (p=0.015). Dose- and volume-staged SRS represent an alternative treatment approach for large AVMs. Dose staging can either be delivered as hypofractionated stereotactic radiotherapy (HSRT) or repeat SRS. Volume-staged SRS partitions the AVM into geometrically distinct portions that are treated over time until the entire AVM is irradiated. A systematic literature review performed to compare the outcomes of dose-staged and volume-staged SRS in the treatment of large AVMs (>10 cm^3) found the mean complete obliteration rates for the dose- and volume-staged groups were 22.8% and 47.5%, respectively. Complete obliteration was seen in 18.6% and 49.2% of patients in the dose- and volume-stage groups, respectively. The mean rates of symptomatic radiation-induced changes were 13.5% and 13.6% in dose- and volume-staged groups, respectively. The mean rates of cumulative post-SRS latency period hemorrhage were 12.3% and 17.8% in the dose- and volume-staged groups, respectively.[24] Finally, the mean rates of post-SRS mortality were 3.2% and 4.6% in dose- and volume-staged groups, respectively. Study findings were limited by the significant variability of the radiosurgical parameters in the dose- and volume-staged SRS series included for analysis. Therefore, a definitive conclusion about the superiority of one treatment approach over the other cannot be made. Proton beam therapy is a treatment alternative for large AVMs because it has been shown to produce a high occlusion rate.[25,26]

Pre-SRS Embolization. Preoperative embolization can be used for volumetric reduction and targeted embolization for obliteration of AVM-related aneurysms and fistulae.[27] However, embolization before SRS has been reported to negatively affect obliteration rates.[28-30] Russell et al. conducted a literature review and meta-analysis to compare the outcomes of AVMs treated with embolization plus SRS and those of AVMs treated with SRS alone.[31] Twelve articles including 1,716 patients were eligible for

analysis. The meta-analysis showed that AVM treatment with embolization plus SRS as compared with SRS alone resulted in a significantly lower obliteration rate (OR 0.51, p<0.00001), with pooled obliteration rates of 48% for the embolization plus SRS group versus 63% for the SRS alone group. Although no significant heterogeneity was found in the meta-analysis, the authors reported observable heterogeneity between the study populations, AVM volumes, SRS parameters, embolic agents and SRS modalities, thus limiting generalizability of study findings. The negative impact of embolization on radiosurgery may be explained by attenuation or scattering of radiation beams by embolic material, increased difficulty of radiosurgical targeting, decreased radiosensitivity with concomitant increased angiographic activity, and recanalization of the nidus following embolization.[30] The optimal time between prior embolization and radiosurgery is unknown. However, on the recommendation of the International RadioSurgery Association (IRSA), waiting for a period of several weeks is beneficial to reduce the likelihood of vascular ischemic complications or residual cerebral edema.[32]

Adverse Radiation Effects. During the latency period following SRS, symptomatic changes attributable to adverse radiation effects occur in approximately 10% of patients, depending on AVM location, target volume, and margin dose.[17] It is recommended that patients receive a corticosteroid such as dexamethasone or methylprednisolone following SRS to improve some of these symptomatic adverse radiation effects.[17,32] Patients can continue to take other medications such as antiepileptics and analgesics, during and after SRS according to physician instructions.

Follow-up Imaging. Following SRS, serial clinical exams and MRI are recommended for the first 3 years to monitor treatment effects.[32,33] If MRI at the 3-year mark suggests complete obliteration of the AVM nidus, angiography should be requested to confirm the obliteration. Angiography is considered the gold standard for evaluating post-SRS obliteration because of its high spatial and temporal resolution.[34,35] If MRI before 3 years suggests nidus obliteration, angiography is generally postponed until 3 years have passed.[32,33]

Repeat SRS. If angiography after 3 years shows that the nidus is not obliterated, repeat SRS may be considered. Several studies have shown that in approximately 60% to 70% of patients with incomplete obliteration of AVMs after initial SRS, total obliteration is achieved after repeat SRS.[36-38] Awad et al. performed a systematic review of repeat SRS for AVMs.[39] A total of 14 studies comprising 733 patients were included. The mean obliteration rate for the repeat radiosurgery treatments were 61% and 61.5%, respectively. The median follow-up ranged from 19.5 to 80 months. Time to complete obliteration after the repeat treatment ranged from 21 to 40.8 months. The most common complications of repeat SRS included hemorrhage (7.6%) and radiation-induced changes (7.4%).

Trigeminal Neuralgia

TN is a rare, chronic pain condition that affects the trigeminal or 5th cranial nerve that carries signals between the brain and the face. Neurovascular compression at the root entry zone of the trigeminal nerve in the cerebellopontine cistern is believed to be one of the underlying causes of TN. TN has an

annual incidence of 4 to 5 per 100,000 people,[40] affects more women than men, and is usually observed in people over the age of 50. Symptoms of TN range from a constant ache to recurrent, stabbing pain in the jaw or face that can feel like an electric shock, typically affecting only one side of the face. Pain is often triggered by activities of daily life such as talking, brushing teeth, and chewing. Pharmacotherapy is the first line of treatment of most patients with TN (e.g. carbamazepine, oxcarbazepine, baclofen). For patients who are medically refractory, surgery (e.g. microvascular decompression, rhizotomy, peripheral neurectomy), or SRS may be offered.

Current data about SRS for TN are largely observational. Three of the larger observational studies (≥100 patients) have reported complete or partial pain relief at 1 year ranging from 77% to 85.6% of patients.

To analyze the effects of dose escalation on treatment outcomes in patients undergoing SRS for TN, Kotecha et al conducted a retrospective review of 870 patients.[41] Patients were divided into three groups based on their treatment dose: ≤82 Gy, 83 to 86 Gy, and ≥90 Gy. Median follow-up was 36.5 months from the time of SRS. The 4-year rate of excellent to good pain relief was 87%. The 4-year rate of pain response was 79%, 82%, and 92% in patients treated to ≤82 Gy, 83 to 86 Gy, and ≥90 Gy, respectively. Patients treated to doses ≤82 Gy had an increased risk of pain failure after SRS, compared with patients treated to ≥90 Gy (HR 2.0, p=0.0007). Rates of treatment-related facial numbness were similar among patients treated to doses ≥83 Gy.

The only published RCT on the topic of radiosurgery and TN tested the hypothesis that increasing the nerve length within the treatment volume for TN would improve pain relief.[42] In the study patients with typical TN were randomized to retrogasserian GK radiosurgery (75 Gy maximal dose with 4-mm diameter collimators) using either 1 (N=44) or 2 (N=43) isocenters. With a median follow-up of 26 months the investigators found that irradiating a longer nerve length with a second isocenter didn't improve pain control, but did increase complications (i.e. new or increased postradiosurgery numbness or paresthesia; p=0.018).

Temporal Lobe Epilepsy

TLE accounts for approximately 60% of all people living with epilepsy. There are two types of TLE that are defined by the part of the temporal lobe in which it originates: medial (inner region) and neocortical (side region), with the former being the most common. The seizures that occur with TLE are called either simple partial seizures, in which a person remains conscious, or complex partial seizures, in which a person loses consciousness. A seizure originating in the temporal lobe may be preceded by an aura or warning symptoms, such as: hallucinations; déjà vu; intense emotions; and, a rising sensation in the abdomen. The cause of TLE often remains unknown. However, there are several risk factors, including: traumatic brain injury; infections (e.g. encephalitis, meningitis); blood vessel malformations in the brain; strokes; brain tumours; and, genetics. Most people with TLE respond to anti-seizure drugs, but for those who don't respond to medication, surgery or SRS are treatment options. SRS has been proposed as an alternative to conventional temporal lobectomy for patients who want to avoid surgery or to high-risk patients who are unsuitable for traditional surgery.

The phase 3 trial, Radiosurgery or Open Surgery for Epilepsy (ROSE) sought to directly compare efficacy, morbidities, and cost of radiosurgery versus open surgery for mesial TLE, but was stopped because of poor enrollment.[43] While the researchers aimed to recruit 234 patients to show radiosurgery's noninferiority to open surgery, only 58 patients were enrolled and completed the study. Pre-publication results suggest that radiosurgery is inferior because more patients were seizure-free during the last year of the trial if they had surgery versus radiosurgery (78% vs. 52%), but the study's lack of statistical power makes it impossible to verify that conclusion.[44]

An earlier pilot study by the same investigators, randomized 30 patients with unilateral mesial TLE to either 20 or 24 Gy, targeting the amygdala, hippocampus, and parahippocampal gyrus.[45] Both groups showed significant reductions in seizures by 1 year after treatment. At the 36-month follow-up visit, 67% of patients were free of seizures for the prior 12 months (20 Gy: 58.8%; 24 Gy: 76.9%). Use of steroids, headaches, and visual field defects were not reported to differ by dose or seizure remission. New headaches occurred in 85% of the patients in the high-dose group and 58% of the patients in the low-dose group. Although this difference was not statistically significant, the study was not powered to show differences in adverse events. The prevalence of verbal memory impairment was 15%, and the prevalence of significant verbal memory improvements was 12%.

A 2016 meta-analysis of 13 studies in which the safety and efficacy of radiosurgery for the treatment of mesial TLE was evaluated found that approximately half of the patients were seizure free over a follow-up period that ranged from 6 months to 9 years, with an average of 14 months to seizure cessation.[46] However, all of the included studies were single-arm observational studies, and significant study heterogeneity was detected. Heterogeneity was related to various study factors including doses, patient populations, targets, volumes, and follow-up time.

In one of the largest prospective studies of the efficacy and safety of GKS in the treatment of drug-resistant epilepsies of mesial temporal lobe origin, 21 patients were treated with a marginal dose of 24±1 Gy, corresponding to the 50% isodose curve.[47] The radiation dose to the brainstem was reduced to a minimum volume within the 25% isodose curve, and the optical tract never received a dose of more than 8 Gy. The median seizure frequency of 6.16 the month before treatment was reduced to 0.33 at 2 years after treatment. At 2 years, 65% of the patients were seizure free. Five patients had transient side effects (depression, headache, nausea, vomiting, and imbalance). There was no permanent neurological deficit reported except 9 visual field deficits, and at the 2-year follow-up visit, no patient had worsening in neuropsychological testing as compared with the baseline.

Movement Disorders

Movement disorders are a group of neurological conditions commonly described by increased, decreased or slowed movements.[48] Common types of movement disorders include ataxia, cervical dystonia, chorea, dystonia, functional movement disorder, Huntington's disease, multiple system atrophy, myoclonus, Parkinson's disease, parkinsonism, progressive supranuclear palsy, restless leg syndrome, tardive dyskinesia, Tourette syndrome, tremor and Wilson's disease.[48] The most common movement disorders are essential tremor (ET) and Parkinson's disease (PD).

Severe tremors, such as ET and tremor-dominant PD, have been treated with low rates of complications using Gamma Knife thalamotomy (GKT); however the level of evidence is low with mainly retrospective and prospective studies with less than 100 patients. No multicenter, double-blind, randomized, long-term follow-up studies have evaluated GKT use in movement disorders.

The largest study to date is a retrospective study of 161 patients undergoing nucleus ventralis intermedius (VIM) thalamotomy (with Leksell Gamma Knife) of disabling ET. Young *et al.* (2010) observed statistically significant decreases ($p<0.0001$) in tremor scores for both writing and drawing. Permanent or temporary neurological side effects occurred in 6 and 8 patients, respectively, accounting for 6.9% of the 203 treatments.[49] Retrospective and prospective trials support a decrease in tremor score after GKT,[49-53] with the exception of one prospective trial showing no improvement in tremor ratings after GKT.[54]

Evidence supports SRS thalamotomy as an alternative treatment of intractable tremors for patients who are considered high-risk for conventional surgery such as the elderly or individuals with contraindications to deep brain stimulation or stereotactic radiofrequency thalamotomy.[50-53] A single maximum dose of 130 to 140 Gy to the VIM of the thalamus is the recommended dose.[49-55]

SRS pallidotomy in PD is not recommended based on the relatively high complication rate arising from the anatomical position of the globus pallidum.[55]

References

1. Kondziolka D, Shin SM, Brunswick A, Kim I, Silverman JS. The biology of radiosurgery and its clinical applications for brain tumors. Neuro Oncol 2015 Jan;17(1):29-44.

2. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta chirurgica Scandinavica 1951;102(4):316-9.

3. Chen C, Chapman P, Loeffler J. Stereotactic Cranial Radiosurgery. 2016; Available at: https://www.uptodate.com/contents/stereotactic-cranial-radiosurgery?source=search_result&search=stereotactic%20radiosurgery&selectedTitle=1~145. Accessed June/12, 2017.

4. Schwartz M. Stereotactic radiosurgery: comparing different technologies. CMAJ 1998;158(5):625-8.

5. Canadian Agency for Drugs and Technologies in Health. Gamma knife surgery compared with linac-based radiosurgery systems in the treatment of intracranial lesions or tumours and functional neurosurgery: A review of the precision, accuracy, clinical effectiveness, cost-effectiveness, and guidelines. 2014;Rapid Response Report.

6. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004 May 22;363(9422):1665-1672.

7. Kondziolka D, Lunsford LD, Loeffler JS, Friedman WA. Radiosurgery and radiotherapy: Observations and clarifications. J Neurosurg 2004;101(4):585-589.

8. American Heart Association. What is an arteriovenous malformation (AVM)? 2017; Available at: http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/HemorrhagicBleeds/What-Is-an-Arteriovenous-Malformation-AVM_UCM_310099_Article.jsp#.

9. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. J Neurosurg 2013 February 01;118(2):437-443.

10. Speizler RF, Martin NA. A proposed grading system for arteriovenous malformations. 1986. J Neurosurg 2008 January 01;108(1):186-193.

11. Friedlander RM. Clinical practice. Arteriovenous malformations of the brain. N Engl J Med 2007 June 28;356(26):2704-2712.

12. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014 Feb;58(3):309-318.

13. van Beijnum J, van der Worp, H B, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. JAMA 2011 November 09;306(18):2011-2019.

14. Rubin BA, Brunswick A, Riina H, Kondziolka D. Advances in radiosurgery for arteriovenous malformations of the brain. Neurosurgery 2014 Feb;74 Suppl 1:50.

15. Maruyama K, Kawahara N, Shin M, Tago M, Kishimoto J, Kurita H, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med 2005 Jan 13,;352(2):146-153.

16. International Radiosurgery Association. Stereotactic Radiosurgery for Patients with Pituitary Adenomas. 2004; Available at: http://www.irsa.org/Pituitary%20Guideline.pdf. Accessed July/20, 2017.

17. Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, et al. Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2017 August 01;48(8):e224.

18. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet 2014 February 15;383(9917):614-621.

19. Lang M, Moore NZ, Rasmussen PA, Bain MD. Treatment Outcomes of A Randomized Trial of Unruptured Brain Arteriovenous Malformation-Eligible Unruptured Brain Arteriovenous Malformation Patients. Neurosurgery 2017 October 10.

20. Rutledge WC, Abla AA, Nelson J, Halbach VV, Kim H, Lawton MT. Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. Neurosurg Focus 2014 September 01;37(3):E8.

21. Ding D, Starke RM, Kano H, Mathieu D, Huang P, Kondziolka D, et al. Radiosurgery for Cerebral Arteriovenous Malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-Eligible Patients: A Multicenter Study. Stroke 2016 February 01;47(2):342-349.

22. Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. Int J Radiat Oncol Biol Phys 1996 November 01;36(4):873-879.

23. Patibandla MR, Ding D, Kano H, Xu Z, Lee JYK, Mathieu D, et al. Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study. J Neurosurg 2017 September 08:1-10.

24. Moosa S, Chen CJ, Ding D, Lee CC, Chivukula S, Starke RM, et al. Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. Neurosurg Focus 2014 September 01;37(3):E18.

25. Blomquist E, Engstrom ER, Borota L, Gal G, Nilsson K, Lewen A, et al. Positive correlation between occlusion rate and nidus size of proton beam treated brain arteriovenous malformations (AVMs). Acta Oncol 2016;55(1):105-112.

26. Vernimmen FJ, Slabbert JP, Wilson JA, Fredericks S, Melvill R. Stereotactic proton beam therapy for intracranial arteriovenous malformations. Int J Radiat Oncol Biol Phys 2005 May 01;62(1):44-52.

27. Plasencia AR, Santillan A. Embolization and radiosurgery for arteriovenous malformations. Surg Neurol Int 2012;3(Suppl 2):S104.

28. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP. Radiosurgery for patients with unruptured intracranial arteriovenous malformations. J Neurosurg 2013 May 01;118(5):958-966.

29. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP. Radiosurgery for low-grade intracranial arteriovenous malformations. J Neurosurg 2014 August 01;121(2):457-467.

30. Ding D, Yen CP, Starke RM, Xu Z, Sheehan JP. Radiosurgery for ruptured intracranial arteriovenous malformations. J Neurosurg 2014 August 01;121(2):470-481.

31. Russell D, Peck T, Ding D, Chen CJ, Taylor DG, Starke RM, et al. Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis. J Neurosurg 2017 May 12:1-11.

32. International RadioSurgery Association. Stereotactic radiosurgery for patients with intractable typical trigeminal neuralgia who have failed medical management. International RadioSurgery Association 2009 January.

33. Niranjan A, Kano H, Lunsford LD. Gamma Knife Radiosurgery for Brain Vascular Malformations. : Karger Medical and Scientific Publishers; 2012.

34. Oppenheim C, Meder JF, Trystram D, Nataf F, Godon-Hardy S, Blustajn J, et al. Radiosurgery of cerebral arteriovenous malformations: is an early angiogram needed? AJNR Am J Neuroradiol 1999 March 01;20(3):475-481.

35. Steinberg GK, Fabrikant JI, Marks MP, Levy RP, Frankel KA, Phillips MH, et al. Stereotactic heavy-charged-particle Bragg-peak radiation for intracranial arteriovenous malformations. N Engl J Med 1990 July 12;323(2):96-101.

36. Karlsson B, Kihlstrom L, Lindquist C, Steiner L. Gamma knife surgery for previously irradiated arteriovenous malformations. Neurosurgery 1998 January 01;42(1):6.

37. Maesawa S, Flickinger JC, Kondziolka D, Lunsford LD. Repeated radiosurgery for incompletely obliterated arteriovenous malformations. J Neurosurg 2000 June 01;92(6):961-970.

38. Yen CP, Jain S, Haq IU, Jagannathan J, Schlesinger D, Sheehan J, et al. Repeat gamma knife surgery for incompletely obliterated cerebral arteriovenous malformations. Neurosurgery 2010 July 01;67(1):64; discussion 64.

39. Awad AJ, Walcott BP, Stapleton CJ, Ding D, Leed C, Loeffler JS. Repeat radiosurgery for cerebral arteriovenous malformations. J Clin Neurosci 2015 Jun;22(6):945-950.

40. Katusic S, Williams DB, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945-1984. Neuroepidemiology 1991;10(5-6):276-281.

41. Kotecha R, Kotecha R, Modugula S, Murphy ES, Jones M, Kotecha R, et al. Trigeminal Neuralgia Treated With Stereotactic Radiosurgery: The Effect of Dose Escalation on Pain Control and Treatment Outcomes. Int J Radiat Oncol Biol Phys 2016 September 01;96(1):142-148.

42. Flickinger JC, Pollock BE, Kondziolka D, Phuong LK, Foote RL, Stafford SL, et al. Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study. Int J Radiat Oncol Biol Phys 2001 October 01;51(2):449-454.

43. Radiosurgery or Open Surgery for Epilepsy Trial (ROSE). 2016; Available at: https://clinicaltrials.gov/ct2/show/NCT00860145.

44. Fiore K. Gamma Knife Unlikely to Beat Epilepsy Surgery - But no conclusions can be drawn from underpowered ROSE trial. 2016; Available at: https://www.medpagetoday.com/meetingcoverage/aes/61903.

45. Barbaro NM, Quigg M, Broshek DK, Ward MM, Lamborn KR, Laxer KD, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. Ann Neurol 2009 February 01;65(2):167-175.

46. Feng ES, Sui CB, Wang TX, Sun GL. Stereotactic radiosurgery for the treatment of mesial temporal lobe epilepsy. Acta Neurol Scand 2016 December 01;134(6):442-451.

47. Regis J, Rey M, Bartolomei F, Vladyka V, Liscak R, Schrottner O, et al. Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia 2004 May 01;45(5):504-515.

48. Mayo Clinic. Movement Disorders: Symptoms and Causes. 2017; Available at: https://www.mayoclinic.org/diseases-conditions/movement-disorders/symptoms-causes/syc-20363893.

49. Young RF, Li F, Vermeulen S, Meier R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. J Neurosurg 2010 June 01;112(6):1311-1317.

50. Kondziolka D, Ong JG, Lee JY, Moore RY, Flickinger JC, Lunsford LD. Gamma Knife thalamotomy for essential tremor. J Neurosurg 2008 January 01;108(1):111-117.

51. Ohye C, Higuchi Y, Shibazaki T, Hashimoto T, Koyama T, Hirai T, et al. Gamma knife thalamotomy for Parkinson disease and essential tremor: a prospective multicenter study. Neurosurgery 2012 March 01;70(3):6.

52. Kooshkabadi A, Lunsford LD, Tonetti D, Flickinger JC, Kondziolka D. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. J Neurosurg 2013 April 01;118(4):713-718.

53. Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, et al. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology 2015 November 03;85(18):1562-1568.

54. Lim SY, Hodaie M, Fallis M, Poon YY, Mazzella F, Moro E. Gamma knife thalamotomy for disabling tremor: a blinded evaluation. Arch Neurol 2010 May 01;67(5):584-588.

55. Chin LS, Regine WF. Principles and Practice of Stereotactic Radiosurgery. 2nd ed. New York, NY, USA: Springer; 2015.

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial CNS Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, neuropathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in April, 2018.

Maintenance

A formal review of the guideline will be conducted in 2019. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

ARUBA	A Randomized Trial of Unruptured Brain Arteriovenous Malformations
AVM	Arteriovenous malformation
CNS	Central nervous system
DBS	Deep brain stimulation
ET	Essential tremor
GK	Gamma Knife
GKS	Gamma Knife Surgery
GKT	Gamma Knife thalamotomy
HR	Hazard ratio
HSRT	Hypofractionated stereotactic radiotherapy
IRSA	International RadioSurgery Association
MRI	Magnetic resonance imaging
PD	Parkinson's disease
RCT	Randomized controlled trial
ROSE	Radiosurgery or Open Surgery for Epilepsy
SM	Spetzler-Martin
SRS	Stereotactic radiosurgery
TLE	Temporal lobe epilepsy
TN	Trigeminal neuralgia
VIM	Ventral intermediate nucleus

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial _____Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of CancerControl Alberta's evidence-based clinical practice guidelines and supporting materials comes from the CancerControl Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Participation of members of the Alberta Provincial CNS Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial CNS Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.