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Stereotactic Radiosurgery: Benign Indications

Effective Date: September, 2017

Alberta Health Services
CancerControl Alberta

Clinical Practice Guideline CNS-013a – 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 non-coplanar 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 benign indications for stereotactic radiosurgery?
2. What are the dose recommendations for SRS and FSRT?

Search Strategy

Peer-reviewed articles were searched August 2016 using PubMed, MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Google Scholar. The following search terms were used: stereotactic radiosurgery [MeSH], SRS, benign [MeSH], gammaknife, linac, linear accelerator, acoustic neuroma [MeSH], vestibular schwannoma [MeSH], pituitary adenoma [MeSH], meningioma [MeSH], craniophyaryngioma [MeSH], and hemangioblastoma [MeSH]. Results were limited to studies published after the year 2000, human

participants, English language, and studies >10 participants. The reference lists of relevant articles were screened for additional articles.

The National Guideline Clearinghouse (NGC, Agency for Healthcare Research and Quality) was searched for clinical practice guidelines related to stereotactic radiosurgery. In addition, the webpages of well-recognized cancer guideline developers were hand-searched to ensure no clinical practice guidelines had been missed.

Target Population

The recommendations outlined in the guideline apply to patients age 18 years or older. A wide range of factors must be taken into account in assessing if SRS is the appropriate course of treatment for the patient. Benign brain tumours that can be treated by SRS include vestibular schwannomas, pituitary adenomas, meningiomas, craniopharyngiomas, and hemangioblastomas.

Recommendations

Vestibular Schwannoma (VS)

1. SRS is a possible first line of treatment in patients with newly diagnosed small- to medium-sized vestibular schwannomas, no significant brainstem compression, and reasonably well preserved hearing. SRS may be a suitable choice for patients who desire preservation of neurological function (cochlear, facial nerve) and a high rate of tumour growth control. SRS is proposed as a modality to slow or stop schwannoma growth.
2. Other management strategies for vestibular schwannomas include observation with imaging and surgical excision. Due to a lack of high quality evidence from randomized control trials (RCTs) comparing treatment modalities for VS, treatment choice should be based on individual factors.
3. SRS is recommended for residual disease following surgery or in the presence of recurrent tumours.
4. Both SRS and FSRT be recommended for the treatment of vestibular schwannoma. There is evidence to support the use of FSRT in the case of large, inoperable lesions.
5. **Recommended dose prescription:**

   SRS: 12-13 Gy to the tumour margin. Dosage is dependent on tumour anatomy (proximity of brainstem), hearing status, tumour volume and estimated adverse radiation risks.

   FSRT: total dose of 45-54 Gy at 1.8-2 Gy/fraction

Pituitary Adenomas

6. SRS or FSRT is recommended for the treatment of residual or recurrent non-functioning pituitary adenomas (NFPAs) to lower the risk of subsequent tumour progression. Early

treatment (<6 months post-resection) may decrease the rate of tumour progression of subtotally resected NFPAs.

7. SRS may be considered as a primary treatment in patients with an adenoma that resides in the cavernous sinus and for whom resection is unlikely to result in a reduction of overall tumour volume.
8. SRS is the recommended second line of treatment after surgical resection for acromegaly and Cushing's disease, and the third line of treatment for prolactinomas after dopamine agonists and surgical resection.
9. For patients taking pharmacologic treatment to reduce hormonal secretion by the adenoma (e.g. dopamine agonist or somatostatin analog), discontinuation one month prior to and one month following radiosurgery is recommended.
10. **Recommended dose prescription:**

    SRS: NFPAs should receive a margin dose of 12-18 Gy. Functioning adenomas should receive 15-30 Gy. The optic apparatus should be kept below 8-10 Gy.
    FSRT: total dose of 54-55 45-50.4 Gy at 1.8-2 Gy/fraction

Meningiomas

11. Management strategies for meningiomas include observation, resection, or radiation therapy. Asymptomatic patients can be managed by observation. If therapy is indicated, standard treatment is gross total surgical resection or radiation therapy.
12. SRS may be first option in small meningiomas presumed to be WHO grade I. SRS is recommended for small- to medium-sized benign lesions with distinct margins and at sufficient distance from functionally important or radiosensitive structures.
13. FSRT may be considered as an alternative treatment for WHO grade I meningiomas when there is concern for normal tissue injury, either because of large tumour size or proximity to critical adjacent normal structures or organs at risk (OAR).
14. **Recommended dose prescription:**

    SRS: WHO Grade I meningiomas should receive 12-16 Gy in a single fraction where appropriate.

    FSRT: Total dose of 50-55 Gy at 1.8-2.0 Gy/fraction

Other:

15. SRS can be considered for other indications such as craniopharyngiomas and hemangioblastomas. Individual patient cases should be discussed with a multidisciplinary team at tumour board rounds.

Discussion

1. Vestibular Schwannoma

Vestibular schwannomas (VS), also known as acoustic neuromas, are Schwann cell-derived benign tumours most commonly found in the vestibular portion of the eighth cranial nerve (CN VIII). They account for approximately 8% of intracranial tumours and 80-90% of cerebellopontine angle tumours in adults.[8] They are generally slow-growing and are unilateral in more than 90% of cases, presenting in right and left sides equally.[8] Progressive unilateral hearing decline is the most common symptom that leads to diagnosis of VS.[9] Treatment options include microsurgical removal, radiosurgery, fractionated radiotherapy, and monitoring under observation. There is limited high level evidence comparing the three treatment options; a Cochrane Systematic Review from 2014 found no evidence from RCTs suggesting one method was superior to another, concluding that treatment needs to be selected based on an individual basis, taking into account patient preference, clinician experience, and resources.[10] Furthermore, there are no RCTs comparing different stereotactic RT techniques.[8] As such, any of the treatment methods are an option for VS patients, with consideration given to tumour size, hearing level, and patient's overall physical state.

SRS vs observation: A systematic review of 26 studies including 1340 patients examined the natural history of VS. The overall frequency of growth during a mean follow-up period of 38 months was 46% (95% CI 43-48%), with 8% of all patients regressing (95% CI 6-10%). Eighteen percent of cases required treatment during follow-up (95% CI 16-21%). The mean annual tumour growth rate was 1.2mm/year.[11] Due to the slow growth rate of most vestibular schwannomas, observation may be an option for older patients who are poor candidates for surgery or SRS. However, conservative management is associated with risk of progressive hearing loss. A systematic review of 35 studies examining hearing outcome after VS observation found that patients with tumour growth rate $\leq$2.5mm/year had a significantly higher rate of hearing preservation in comparison to those with a higher growth rate.[12] Breivik et al. allocated patients to SRS (n=113) or conservative management (n=124) based on patient choice and an established treatment algorithm. Despite finding similar rates of hearing loss in both groups, SRS significantly reduced tumour growth rate (and the subsequent need for retreatment).[13] For enlarging tumours that are not candidates for surgery, SRS is a safe and effective treatment option.

SRS vs surgical resection: There are no randomized control trials comparing microsurgery with SRS, and such a study is unlikely due to the slow growth rate of VS and the strong role of patient choice in treatment. Currently, the best available evidence is found with observational and prospective series.

Reported tumour control rates for SRS and microsurgery are comparable; however, there is evidence that the preservation of serviceable hearing is higher following SRS than surgery.[14,15] A systematic review by Wolbers et al.[16] highlights several other well designed observational studies that identify SRS as a better treatment method for facial nerve and hearing outcomes.[17-19] Pollock et al. found normal facial movement and preservation of serviceable hearing was more frequent in an SRS group

(n=46) at three months (p<0.001), 1-year (p<0.001), and at last follow-up (p<0.01) compared to a surgical resection group (n=36).[17] Myrseth et al. reported similar results for hearing function and facial nerve preservation after 2 years of follow-up.[18] A retrospective study with matched controls found that SRS was more effective than resection in measurable hearing preservation (57.5% vs 14.4%, p=0.01) and that patients undergoing resection had higher rates of facial and trigeminal neuropathy (p=0.008 and p=0.009, respectively).[19] There is long-term data to support SRS as the preferred method for hearing preservation; an analysis of 16 studies with a follow-up of at least 5 years found SRS resulted in significantly better long-term hearing preservation outcome rates than microsurgery (p<0.001), but showed no difference in long term tumour control (p=0.122).[14] Roos et al. followed 44 VS patients for ≥10 years and reported a progressive decline in hearing preservation (57% at 5 years and 24% at 10 years follow-up).[20] It is important to note that while hearing loss in VS patients is often evident immediately after surgery, hearing loss can increase markedly over time following SRS.

Tumour control and dose: For the SRS treatment of VS, a dose of 12-13 Gy is typically prescribed to the 50% (or other) isodose line that conforms to the 3D tumour margin. The most common dose is 12.5 Gy, which is often prescribed to maximize hearing preservation in patients with smaller tumours.[9] Historically, doses were higher (up to 22 Gy), yielding excellent tumour control but high rates of cranial nerve toxicities and low rates of hearing preservation.[8] More recent single-centre studies using a marginal dose of 12-13 Gy to treat tumours up to 3 cm in diameter have reported local control rates of 91-100%.[21] A meta-analysis by Rykaczewski et al. compared studies published from 1998-2007 and 2007-2011 and established that the average dose applied to the periphery of the tumour was lower (12.4 Gy) 2007-2011 series than the earlier series (14.2 Gy), and the hearing preservation was higher (66.45% vs 51.0%).[22] The reported tumour growth control in the later studies was 92.7%.[22]

A long-term study examining the safety and effectiveness of SRS after more than 10 years in 440 patients reported actuarial 5 and ≥10 year progression-free survival (PFS) rates of 93% and 92%, respectively. The median marginal dose was 12.8 Gy and no patient developed treatment failure more than 10 years after treatment. The 10-year facial nerve preservation rate was 97% in the high marginal dose group (>13 Gy) and 100% in the low marginal dose group (≤13 Gy).[23] The University of Pittsburgh reported their 15-year experience of 829 patients who underwent GKRS. The average tumour volume was 2.5 cm^3 and median margin dose to the tumour was 13 Gy (range 10-20 Gy). Tumour control rates at 10 years were 97%, hearing preservation was possible in 50-77% of patients, facial neuropathy risks were <1%, and trigeminal symptoms were detected in <3% of patients whose tumours reached the trigeminal nerve.[24] The consensus of the Alberta Provincial CNS Tumour Team is to apply a dose of 12-13 Gy to the tumour margin, taking into consideration tumour anatomy (proximity of brainstem), hearing status, tumour volume and estimated adverse radiation risks (recommendation #6).

FSRT: Both SRS and FSRT have been extensively used to treat VS. The goal of FSRT is to reduce radiation injury to critical neural structures (such as commonly injured cranial nerves V, VII, VIII) and preserve tumour control. While SRS requires targets with a spherical shape, FSRT allows for a more

conformal dose distribution around irregularly shaped targets, avoiding hot spots and increasing tolerance for organs at risk.[15] Multiple studies have demonstrated the general safety and efficacy of this approach. A multicenter retrospective study of 449 patients with VS found no difference in local control between tumours treated with FSRT (n=291) and those treated with SRS (n=169) at 36 months, 60 months, and 120 months (97%, 95%, and 94% respectively, p=0.39).[25] The median dose for FSRT was 57.6 Gy in 1.8 Gy/fractions, and 13 Gy for SRS. Several other single-centre series have found no significant difference in tumour control between VS patients treated with SRS and FSRT,[26-29] although one study reported superior hearing preservation rates with FSRT,[27] and another reported a small benefit in trigeminal nerve preservation rate with FSRT.[29] In cases where the physician feels FSRT is an appropriate choice for the patient, a total dose of 45-54Gy at 1.8-2Gy/fraction should be used (recommendation #6).

Hearing preservation: Roos et al. followed 44 patients treated with SRS for $\geq$10 years and confirmed a crude tumour control rate of 97.7%, but reported a continual decrease in hearing preservation (5- and 10-year hearing preservation rate of 57% and 24%, respectively).[20] A systematic review by Fong et al. found no significant difference in hearing preservation rates between SRS and FSRT studies that reported average tumour volumes less than 3cm^3 (73.3% vs 77.8%, p=0.2071). In the studies that reported average tumour volumes $\geq$3cm^3, hearing preservation rates were greater in patients who received FSRT as compared to SRS (94% compared to 71%, p=0.0210).[30] Older age, larger tumour volume, radiotherapy dose to the cochlea, and greater degree of baseline hearing loss have been found to be risk factors for hearing loss with SRS treatment.[8,31-33] For these patients, FSRT could be a preferable treatment option.

2. Pituitary Adenomas

Pituitary adenomas are benign tumours that arise from the cells of the anterior pituitary gland. Pituitary tumours are fairly common in the general population; a meta-analysis of 10 radiographic and post-mortem studies involving 3577 patients reported an overall prevalence of 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies).[34] First-line treatment for pituitary adenomas is typically surgery or pharmacologic treatment; however, when one of these interventions fails or there is a recurrence, radiation therapy using SRS or FSRT should be considered. Upfront SRS may also be considered in select circumstances. For a more detailed review on treatment options for pituitary adenomas, please see AHS guideline Pituitary Adenomas.

Non-functioning pituitary adenomas (NFPA): NFPAs are adenomas that do not secrete active hormones. They represent approximately one-third of all pituitary tumours.[35] The primary treatment goal for NFPAs is tumour control, and surgical resection is typically the first-line management strategy. Radiation therapy in the form of SRS or FSRT should be considered for clinical NFPAs when residual adenoma remains after surgery or when residual adenoma regrows after surgery. When obvious adenoma tissue remains after resection, continued growth is approximately 30-60% at five years.[36] Therefore, the goal of radiation therapy in NFPAs is to halt tumour growth and lower the risk for subsequent tumour progression.

Reported rates of tumour control range from 94-100%.[37] A multicenter retrospective study of 512 patients with NFPA (median tumour volume 3.3 cm^3) treated with SRS (median dose 16 Gy) reported an overall tumour control of 93.4%. Actuarial PFS rates were 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years respectively.[38] Adenomas less than or equal to 5 cm^3 were associated with better PFS (OR 1.08, 95% CI 1.02-1.13, p = 0.006).[38] Similar tumour control rates have been reported in other retrospective series, both as a second line of treatment and as primary treatment.[39,40] These studies have also noted the diminished effects of tumour control with larger volume adenomas. A systematic review by Chen et al. examined 17 studies to determine the efficacy and safety of GKRS for NFPAs based on tumour volume. The authors found significant differences in rate of tumour control and radiosurgery-induced endocrinological deficits after stratifying by tumour volume (p<0.001). SRS was the optimal choice for the treatment of 'medium volume' NFPAs that are medium volume (2-4mL), and tumours that were greater than 4mL had the highest rates of radiosurgery-induced endocrinological deficits (22%) and lowest rates of tumour control (91%). As a result, the authors conclude that patients with residual tumour volumes of <4mL will benefit most from SRS treatment.[41] For this group, tumour control was high (96-99%), rate of optic neuropathy injury was minimal (0-1%) and rate of endocrinological deficits was low (1-7%).[41]

Early treatment (<6 months post-resection) may decrease the rate of tumour progression of subtotally resected NFPAs. Pomeraniec et al. compared outcomes in NFPA patients who received SRS $\leq$ 6 months after surgery (n=32) and >6 months after surgery (n=32). Greater risk of tumour progression was found in the late radiosurgical group (p=0.027) over a median follow-up period of 68.5 months.[42] Furthermore, the late radiosurgical group had high occurrence of post-SRS endocrinopathy (p=0.041). The authors concluded that delaying SRS may place the patient at increased risk for adenoma progression and endocrinopathy.[42] It is the consensus of the AHS CNS Provincial Tumour Team to aim for early treatment following resection; however, due to limited evidence, further investigation into the timing of FSRT and SRS is warranted.

Dose prescription. A margin dose of 12-18 Gy is frequently used for SRS for NFPAs; however, dose selection should be made based on the tolerance of adjacent structures. The optic apparatus is generally believed to be the structure most sensitive to SRS. Accordingly, several guidelines suggest a limited dose to the optic pathway (no more than 8-10 Gy).[36,43] A systematic review by Sheehan et al. found that common fractionated doses to pituitary adenomas are 45-54 Gy at 1.8-2 Gy per fraction per day.[35] Of the studies reviewed, tumour control varied from 74-100%. There is no Class I evidence comparing FSRT and SRS for NFPAs, therefore, physicians must choose a radiation treatment modality that allows for a highly targeted irradiation of the adenoma while achieving a tolerable dose to adjacent critical structures.

SRS as primary management of NFPAs. SRS or FSRT can be performed as the primary management options in carefully selected patients, including those who have significant comorbidities, are at an advanced age, or choose not to undergo surgery. Lee et al. reported the outcomes of 41 patients who received SRS as a primary treatment for NFPAs. Overall tumour control rate was 92.7%, and the actuarial tumour control rate was 94% at 5 years and 85% at 10 years post-

treatment, suggesting SRS is an acceptable first-line treatment for patients who are unable to undergo surgery.[39] This has been supported in smaller cohort by Hasegawa et al.[44]; however, further research is warranted.

Functioning Pituitary Adenomas: The goal of treatment for functioning pituitary adenomas is to control tumour growth and facilitate endocrine remission, which typically requires a higher dose prescription for SRS. As with NFPAs, the first-line treatment option for functioning pituitary adenomas (except prolactinomas) is surgical resection. SRS is usually indicated for residual tumour following surgery, tumour recurrence, or failure of medical therapy. Functioning pituitary adenomas should receive an SRS dose of 15-30 Gy.

Somatotroph adenoma (acromegaly). In acromegaly cases where there is invasion of the adenoma into surrounding structures (e.g. dura or cavernous sinus), complete resection is not always possible. Radiosurgery is considered when resection and pharmacologic therapy have not been successful in controlling growth hormone secretion or adenoma growth. A review of six retrospective studies with 80 or more patients reported an endocrine remission range of 17-58% at 5 years post-SRS.[37] Hypopituitarism occurred after SRS treatment in 8-32% of patients.[37] Another systematic review of all major acromegaly SRS studies from 2000-2014 reported an average endocrine remission of 43.6% (range 0-82%).[45] Neurologic deficits were reported in 1.8% of patients (range 0-11%) and hypopituitarism occurred in 15.3% of cases (0-40%).[45] In a long-term follow-up study of 35 patients (median follow-up 120 months), Ronchi et al. reported a significant increase in cure rate over time (6% at 3 years, 25% at 7 years, 46% at 10 years, $p<0.005$).[46]

ACTH-secreting pituitary adenoma (Cushing's disease). SRS should be considered for treatment for pituitary adenomas causing Cushing's disease when surgery has been unsuccessful. The primary goals of treatment are to lower adrenocorticotrophic hormone (ACTH) and cortisol secretion. A retrospective review of 96 SRS patients treated with a median dose of 22 Gy reported an endocrine emission rate of 70% at last follow-up (median 48 months).[47] Tumour control was achieved in 98% of patients. The median time to remission was 16.6 months. Median time to remission for patients who temporarily stopped taking ketoconazole while receiving SRS was 12.6 months, and for those who continued to take ketoconazole, 21.8 months ($p<0.012$).[47] Castinetti et al. also found a significant difference in remission rates for patients receiving pharmacologic treatment at the time of SRS; 20% of patients on anticortisolic drugs achieved endocrine remission at final follow-up, compared to 46% of patients who were off drugs ($p=0.02$).[48] SRS has been used to treat Nelson syndrome in the setting of bilateral adrenalectomy.[49,50] Several small studies have found that SRS is an effective adjuvant treatment with relatively few adverse effects; however, further research is needed in order to recommend treatment.

Prolactinoma. The first line of treatment for patients with a prolactinoma is typically with dopamine agonists (such as bromocriptine or carbergoline), and for those who don't respond to medication, surgery.[37] Radiosurgery is the third line of treatment to control tumour growth when medication and surgery have failed. SRS and FSRT studies report similar control rates.[36] A systematic review by Kim

et al. reported 25 Gy as the most commonly reported SRS dose for the treatment of prolactinomas (median range 13-34 Gy).[51] Liu et al. treated 22 patients with a median SRS dose of 15 Gy (range 12-25 Gy) and reported endocrine normalization in 27% of patients and endocrine improvement in 56% of patients.[52] In a separate study, long-term follow-up (median 42.3 months) of 38 patients treated with SRS for prolactinoma reported endocrine remission in 50% and SRS induced hypopituitarism in 30.3% of patients.[53]

Concurrent Pharmacologic Treatment: It is thought that endocrine suppressive medications make tumour cells less susceptible to the damaging effects of radiation therapy. Landolt et al. were first to observe a delay in endocrine normalization in patients with acromegaly who received octreotide during SRS versus those patients who received SRS only.[54] This has been supported by later studies, with similar patterns seen in patients with prolactinomas and Cushing's disease.[47,48,53,55] Sheehan et al. followed 418 pituitary adenoma patients treated with SRS for a minimum period of 6 months. In a subset analysis of patients with acromegaly (n=130) or a prolactinoma (n=32), the probability of remission was 1.71 times greater in patients not receiving pituitary suppressive medication at time of radiosurgery (somatostatin analog or dopamine agonist) than those who were on medication (95% CI 0.96-2.05).[56] Based on these results, the authors adopted a policy at their own institution of temporarily discontinuing pituitary suppressive medications before and after SRS to maximize the potential for achieving endocrine remission. Well-designed RCTs are still needed to confirm the negative relationship between pituitary suppressive medication and outcome following radiosurgery. Currently, it is recommended to suspend all anti-secretory medication one month before and one month after radiosurgery (recommendation #10).

Meningiomas

Meningiomas are the most frequent primary brain tumours, originating in the meninges and accounting for approximately one-third of all primary CNS tumours.[57] Population-based studies estimate that 80-90% of meningiomas are WHO grade I (benign).[58] Management strategies for meningiomas include observation, resection, or radiation therapy. Generally, if therapy is required, the first line of treatment for presumed or known WHO grade I meningiomas is surgical resection. SRS is a treatment option for small tumours and FSRT in large or previously treated tumours.[59,60] In addition, it has been used as a primary treatment option in surgically inaccessible tumours and in patients who are poor surgical candidates due to advanced age or medical comorbidities.[61] Please see the AHS Provincial Guideline 'Meningiomas' for further details on the recommended treatment options for meningioma patients in Alberta.

WHO Grade I: Several recent systematic reviews have demonstrated the safety and efficacy of SRS in the control of benign meningiomas. Tumour control rates are high (92-100%), and are comparable to results with resection.[62] Pollock et al. compared tumour control rates after surgery (n=136) or SRS (n=62) for 198 patients with small- to medium-size meningioma and found tumour progression/recurrence was more frequent in the surgical resection group (12%) than the SRS group

(2%, p=0.04).[63] No statistically significant difference was found for 3- and 7-year PFS between the SRS group and patients with Simpson Grade I resections, but SRS did result in a higher PFS than patients with Simpson Grade 2 and 3 resections. The authors concluded that SRS provides the same degree of tumour control as total resection.[63]

A large-scale retrospective analysis of 4565 patients from 15 European centers reported 5- and 10-year PFS rates of 95.2% and 88.6%, respectively. The median dose to the tumour margin was 14 Gy. Tumour control was higher for imaging defined tumours versus grade I meningiomas (p<0.001), for female versus male patients (p<0.001), and for skull base versus convexity tumours (p<0.001).[64] Kondziolka et al. studied a large cohort of 972 patients with meningiomas treated with a mean dose of 14 Gy. Overall tumour control rate for benign meningiomas (Grade I) was 93%, and at 10 years, Grade I tumours were still controlled in 91% of patients.[65]

Atypical and malignant meningiomas are typically treated with surgical resection.[62] Although there have been a few small series examining the use of SRS or FSRT to treat grade II and III meningiomas,[66-69] the evidence is limited and the tumour must be small to be safely eligible for SRT techniques.[70]

Other Indications

Craniopharyngiomas: Craniopharyngiomas are rare and benign solid or mixed solid-cystic tumours that arise from the residual epithelial cells of Rathke's pouch.[71,72] The first line of therapy for craniopharyngiomas is typically surgical resection;[73,74] however, aggressive surgery can be associated with complications and neurologic injury. SRS/SRT techniques have been increasingly used as a primary option for small tumours away from critical structures, as secondary treatment for residual tumour following conservative surgery, and as an option for recurrent disease.[72-74]

In a study of 137 patients with 162 craniopharyngiomas treated with a median SRS dose of 12 Gy (range 9.5-16), Lee et al. reported actuarial 5- and 10-year PFS rates of 70% and 43.8%. At last follow-up (median 45.7 months), the rates of tumour control were 72.7%, 73.9% and 66.3% for solid, cystic, and mixed tumours, respectively.[71] Among other retrospective series, actuarial 5-year PFS rates range from 67-92%[75-79], and from 52-76% at 10 years.[75-77] Combs et al. treated 40 patients with FSRT using a median target dose of 52.2 Gy (range, 50.4-56 Gy) applied in a median conventional fractionation schedule of 5 x 1.8 Gy per week. At a median follow-up of 98 months, local control was 100% at 5 and 10 years, with 5- and 10- year OS at 97% and 89%, respectively.[80] The authors conclude that FSRT for craniopharyngiomas can result in excellent long term tumour control while sparing surrounding organs at risk.

Hemangioblastomas: Hemangioblastomas are rare, highly vascular tumours of the central nervous system most often found in the posterior fossa.[81] Hemangioblastomas can present as sporadic

lesions (approximately 75% of cases) or as manifestations of von Hippel-Lindau disease (VHL). While sporadic lesions arise primarily in the cerebellum, VHL-associated hemangioblastomas can arise in the cerebellum, spinal cord, and brain stem.[81] Treatment options for hemangioblastomas include surgery and radiation therapy. Surgical resection is generally the first treatment of choice for most symptomatic hemangioblastomas; however, SRS can an appropriate treatment option for patients with multiple tumours and with surgically inaccessible lesions.

A large, international retrospective study evaluated 186 patients who underwent SRS for the treatment of 517 hemangioblastomas. Patients with VHL-associated hemangioblastomas (n=80) received a median margin dose of 18 Gy, while patients with sporadic lesions (n=106) received a median dose of 15 Gy. OS was 94% at 3 years, 90% at 5 years, and 74% at 10 years.[81] The 5-year rate of developing a new tumour was 43% in VHL patients, and the 5-year rate of developing a recurrence from a residual tumour was 24% in sporadic patients.[81] Seven percent of patients developed adverse radiation affects. In another long term study (median follow-up 96 months) of 21 patients with 57 intracranial hemangioblastomas, 5- and 10- year tumour control rates were 67% and 44% for sporadic patients and 97% and 83% for VHL patients, suggesting SRS is an effective treatment method for small, solid, and VHL-associated lesions.[82] In contrast, a prospective evaluation of SRS for the treatment of VHL-associated hemangioblastomas reported a local control rate of 91%, 83%, 61%, and 51% for 2, 5, 10, and 15 years, respectively. Due to the diminishing control over long-term follow-up, the authors suggest that SRS be reserved for the treatment of tumours that are not surgically resectable.[83]

The aforementioned retrospective series suggest that SRS can be a treatment option for growing residual hemangioblastomas, progressive deep-seated tumours that are high risk for surgery, VHL-associated tumours that are not resectable, and recurrences of residual tumours. Since there are no RCTs comparing surgery and SRS, patients are best managed following discussion with a multidisciplinary team at Tumour Board rounds, taking into consideration the size and anatomic location of the lesion.

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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 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 August, 2017.

Maintenance

A formal review of the guideline will be conducted at the Annual Provincial Meeting 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

ACTH, adrenocorticotropic hormone
AHS, Alberta Health Services
CNS, central nervous system
FSRT, fractionated stereotactic radiosurgery
GK, Gamma Knife
GKRS, Gamma Knife radiosurgery
LINAC, linear accelerator
NFPA, non-functioning pituitary adenoma
OAR, organs at risk
PFS, progression-free survival
RCT, randomized control trial
RTOG, Radiation Therapy Oncology Group
SRS, stereotactic radiosurgery
SRT, stereotactic radiotherapy
VHL, von Hippel-Lindau disease
VS, vestibular schwannoma
WBRT, whole brain radiation therapy
WHO, World Health Organization

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS 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*.