Gamma Knife Radiosurgery for Lesions in Uncommon and Critical Locations

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ABSTRACT

Gamma Knife Radiosurgery (GKRS) is a well established therapy for lesions of the Central Nervous System (CNS). It may be considered the gold standard in radiosurgery for CNS lesions. The literature on the subject is vast, yet there are uncommon lesions in critical locations which deserve a closer look. The author presents a review of the literature on GKRS for lesions in uncommon and critical locations and illustrates GKRS for those less common lesions with examples of his own practice.

Keywords: Gamma knife radiosurgery; Location; Uncommon lesion; Meningioma; Schwannoma; Neurocytoma; Subependymoma; Metastases; Cavernous sinus; Intraventricular

Abbreviations: AVM = Arteriovenous Malformation; CC = Cubic Centimeters; CN = Cranial Nerve; CNS = Central Nervous System; CSF = Cerebrospinal Fluid; FU = Follow-Up; GKRS = Gamma Knife Radiosurgery; MRI = Magnetic Resonance Imaging; PA = Pituitary Adenoma; PD = Prescription Dose; SFT = Solitary Fibrous Tumor; TOF = Time-Of-Flight; VS = Vestibular Schwannoma
INTRODUCTION

Currently, approximately one million patients have undergone Gamma Knife radiosurgery worldwide. A PubMed search with the term “Gamma Knife radiosurgery” prompts more than 13’100 publications in scientific medical journals not counting books and chapters. Gamma Knife radiosurgery (GKRS) is the oldest and best documented form of radiosurgery for lesions of the central nervous system (CNS). GKRS is performed using a dedicated machine and it is usually done by neurosurgeons. The literature on common lesions undergoing GKRS such as meningiomas, vestibular schwannomas (VS), pituitary adenomas (PA), metastases, and arteriovenous malformations (AVM) is abundant and does not need to be discussed in detail in this chapter. Yet, there are rare lesions occurring in high-risk locations treated with GKRS which merit special attention.

Uncommon and at the same time high-risk locations for neurosurgical lesions are lesions within or in close proximity to eloquent cortex, cranial nerves (CN), intraventricular lesions, or lesions of the pineal region. Such lesions may pose a considerable therapeutic challenge. They may be of vascular-, neoplastic-, or functional nature. The following pathologies may be involved: brain vascular malformations such as AVMs or cavernomas; extraaxial benign tumors such as meningiomas, schwannomas etc.; intraaxial tumors such as low-grade or high-grade gliomas and metastases; or functional disorders such as paracentral epilepsy. Thorough preoperative planning is mandatory when performing open microsurgery for such lesions. It may go as far as the development of special access trajectories [20] and it may involve preoperative functional MRI (fMRI) with white matter tractography. Intraoperatively, the use of a navigation system and electrophysiological mapping of the cortex will be required [3]. Even if all the challenges are addressed, open microsurgery for such lesions will often be considered too risky for the patient. A valuable alternative seems to be radiosurgery.

This chapter provides an overview regarding current practice of GKRS for uncommon intraaxial, intraparenchymal and extra-axial, extraparenchymal lesions in critical locations. Each of the following sections lists an illustrative case of the author’s own practice.

GAMMA KNIFE RADIOSURGERY FOR MOTOR CORTEX LESIONS

GKRS has been used for the following lesions in close proximity to the motor cortex: arteriovenous malformations (AVM), meningiomas, solitary fibrous tumors (SFT), low-grade or high-grade gliomas, metastases, and paracentral epilepsy [1,7,19,21,23]. GKRS may be applied with and without fMRI.

AVM

AVMs may be located within or in close proximity to eloquent cortex (Figure 1a and Figure 1b). Hadjipanayis CG et al. reported in 2001 on 33 consecutive patients who underwent GKRS...
for AVMs in the motor cortex during a 9-year study period [7]. The mean AVM volume was 4.3 cc, the prescription dose (PD) was 20 Gy to the 50% isodose and the AVM margin. The results were best for patients with AVM volumes of < 3 cc: 87% had complete obliteration. Patients with AVM volumes of 3 - 10 cc had an obliteration rate of 64% and patients with AVM volumes of > 10 cc had an obliteration rate of 25%. One patient (3%) with a 8.4 cc AVM suffered from a newly developed hand weakness following GKRS and one patient died from an intracranial hemorrhage during the latency period between GKRS and the anticipated obliteration at 1-2 years following GKRS. The largest patient group to date is presented by Ding D et al. in 2013 [1]. 134 patients underwent GKRS for primary motor- and sensory cortex AVMs with a median volume of 4.1 cc. The PD was 20 Gy to the 50% isodose and the AVM margin. Again, best results were achieved in patients with AVM volumes of < 3 cc. Their obliteration rate was 80% while it was 55% for AVM volumes > 3 cc. One patient (0.7%) developed new-onset seizures and the overall permanent clinical morbidity rate was 9% following GKRS mostly due to latency period hemorrhage.

Figure 1a: Axial T2-weighted MRI showing a 4.4 cc right frontal AVM extending into the right motor cortex.
**Figure 1b:** Coronal T2-weighted MRI showing the same right frontal AVM as in Figure 1a.

Figure 2a shows a time-of-flight (TOF) MRI of an 44-year old male patient with an AVM within the left motor cortex. The patient had a history of a sudden onset right-sided hemiparesis which resolved within a few weeks. Only after the hemiparesis had resolved, an MRI was done. This showed the small AVM within the left motor cortex and what was considered to be a small residual scar from a former hemorrhage within the left motor cortex. The AVM was fed by the left callosa marginalis artery (Figure 2b) and it was treated with GKRS by the author. The nidus volume was 1 cc and the prescription dose (PD) was 22 Gy to the 50% isodose and the margin of the nidus. At the 6-month follow-up (FU), the AVM was occluded and the patient remained asymptomatic throughout the 6.7-year FU period (Figure 2c).
**Figure 2a:** Axial TOF MRI showing the 1 cc nidus of the AVM at the time of GKRS.

**Figure 2b:** Digital subtraction angiography of the anterior cerebral arteries showing the AVM at the time of GKRS which is fed by the left pericallosal artery. The cross hair artifacts are caused by the fiducial box.
Figure 2c: Axial TOF MRI showing no residual AVM at the 6.7-year follow-up. The occlusion of the AVM was already visible 6 months after the GKRS.

Meningiomas

Parasagittal- or convexity meningiomas in the central region may be challenging tumors for open microsurgery because of a possible venous involvement of Rolandic veins or the superior prasagittal sinus (Figure 3a). In such cases either primary GKRS or secondary GKRS following partial tumor removal for volume reduction may be the treatment of choice. There are no special reports on GKRS for meningiomas in this particular location.

Figure 3a shows the MRI of a 57-year old female patient with a convexity meningioma over the right motor cortex and the central sulcus. The patient was treated by the author with GKRS. The tumor volume was 4 cc and the PD was 12 Gy to the 50% isodose and the tumor margin. At the 6-year FU, the tumor volume was reduced (Figure 3b) and the patient remained asymptomatic.
Figure 3a: Axial T1-weighted MRI with contrast enhancement showing a 4 cc convexity meningioma over the right motor cortex and the central sulcus adjacent to a Rolandic vein at the time of GKRS.
Figure 3b: Axial T1-weighted MRI with contrast enhancement showing the slightly reduced tumor 6 years after GKRS.

**Solitary Fibrous Tumor**

SFTs are rare tumors of the CNS. There are only a few case reports on GKRS for SFT. Yet, it seems that a tight MRI FU-regime combined with readiness to intervene may lead to long-term survival with good neurological function even if the tumor is located next to the motor strip [23].

Figure 4a shows a 1.2 cc SFT of the convexity over the right motor cortex in 62-year old male patient. This tumor was treated with GKRS by the author. The PD was 15 Gy to the 50% isodose and the tumor margin. Figure 4b shows the same region 13 years later. Meanwhile the patient had undergone several craniotomies and radiosurgical treatments for local tumor recurrence. The full history of this case has been published elsewhere [23].
Figure 4a: Axial T1-weighted MRI with contrast enhancement showing a 1.2 cc SFT of the convexity compressing and displacing the right motor cortex and the central sulcus at the time of GKRS.

Figure 4b: Axial T1-weighted MRI with contrast enhancement showing the same region 13 years later.
Low-grade Glioma

To the best of my knowledge, there are no case reports or mini series on GKRS for gliomas adjacent to or within the motor cortex. Figure 5a shows a low-grade glioma adjacent to the right motor cortex in an asymptomatic 31-year old female patient. The patient refused biopsy or surgery of the tumor and underwent upfront GKRS by the author. The tumor volume was 28.4 cc and it was treated with a PD of 11 Gy to the 50% isodose and the tumor margin. Within the first 3 months following GKRS, the patient had focal epileptic seizures regarding the left arm and leg. The seizures were treated medically and they subsided. About 1 year after the GKRS, the antiepileptic medication was discontinued and the patient remained seizure free during the rest of the FU period. At the 7-month FU, the tumor had changed its aspect (Figure 5b) with a new contrast enhancement. This new contrast enhancement was attributed to the radiosurgery treatment and not to a tumor upgrade. Accordingly, the patient underwent no further therapeutic steps. At the 3.5-year FU, the tumor had shrunk significantly and the patient remained asymptomatic for the rest of the FU (Figure 5c).

Figure 5a: Axial T1-weighted MRI with contrast enhancement showing a 28.4 cc low-grade glioma adjacent to the right motor cortex at the time of GKRS.
Figure 5b: Axial T1-weighted MRI with contrast enhancement showing changes of contrast enhancement 7 months following GKRS.

Figure 5c: Axial T1-weighted MRI with contrast enhancement showing the significantly reduced hypointensity at 3.5 years after GKRS.
Metastases

Metastases may occur within the motor cortex (Figure 6a). There is one series with 96 patients on GKRS for metastases in this particular critical area published by Luther N et al. [19]. Motor function improved or remained stable in 81% of the cases and worsened in 19%. New motor deficits developed in 22% of patients who had no motor weakness prior to GKRS.

Figures 6a&b belong to a 47-year old patient with testicular carcinoma who has been published elsewhere [25]. The patient presented with an asymptomatic 0.07 cc metastases within the left motor cortex which was treated by the author with a PD of 25 Gy at the 50% isodose and the tumor margin. The tumor disappeared during FU and the patient remained asymptomatic. One year later, the patient presented with a 0.5 cc metastases within the right motor cortex (Figure 6a). The patient underwent GKRS by the author to the right motor cortex metastasis with a PD of 25 Gy to the 50% isodose and the tumor margin. At the 6-week FU the tumor had almost disappeared and the patient remained asymptomatic (Figure 6b). Ideally, GKRS for metastases within eloquent cortex should be performed before the patient develops neurological deficits or at least as soon as the patient develops such deficits.

Figure 6a: Axial T1-weighted MRI with contrast enhancement showing a 0.5 cc metastasis of a testicular carcinoma within the right motor cortex surrounded by a slight perifocal edema at the time of GKRS. The radiosurgically treated metastasis within the left motor cortex has disappeared.
Paracentral Epilepsy

McGonigal A et al. has published 4 patients who underwent GKRS for intractable epilepsy arising from the central region [21]. None of the patients developed motor deficits and no other radiosurgery-related complications occurred. Two of the patients improved in Engel class and 2 remained unchanged.

GAMMA KNIFE RADIOSURGERY FOR INTRAVENTRICULAR OR PARAVENTRICULAR LESIONS

GKRS has been used for the following intraventricular lesions: meningiomas, neurocytoma, subependymoma, and metastases [2,6,14,15,16,17,27,34].

Meningioma

Kim IY et al. published a series of 9 patients who underwent GKRS for intraventricular meningiomas during a 16-year period [16]. Tumor control was achieved in 7/9 (78%) patients, none developed radiosurgery-related side effects or hydrocephalus. The median tumor volume was 3.9 cc, the median PD was 16 Gy to the 50% isodose and the tumor margin. One patient required repeat GKRS for delayed tumor progression. GKRS for trigonal meningiomas seems to bear a certain risk for the development of a perifocal edema [27]. Yet, with a PD of 18 Gy the authors have applied an unusually high dose in their 2 cases. The authors themselves blame this unusual and unnecessary dose for the edema formation [27]. Since meningiomas WHO I are
usually treated successfully with a PD of 12 to 14 Gy, there is no reason why intraventricular meningiomas should be treated any differently.

Figure 7a shows an intraventricular meningioma in an asymptomatic 68-year old female patient which was treated by the author with GKRS. The tumor volume was 5.4 cc, the PD was 12 Gy to the 50% isodose and the tumor margin. At the 8.7-year FU, the tumor was controlled and the patient remained asymptomatic (Figure 7b). GKRS seems to be a good alternative or supplement to open microsurgery or endoscopic surgery as long as the tumor is not too large and has not yet lead to hydrocephalus.

**Figure 7a:** Axial T1-weighted MRI with contrast enhancement showing a 5.4 cc meningioma in the right lateral posterior ventricle at the time of GKRS.

**Figure 7b:** Axial T1-weighted MRI with contrast enhancement showing the tumor which has not changed in size more than 8 years after GKRS. Meanwhile, new meningiomas have evolved and have also been treated with GKRS.
Neurocytoma

Several groups have published series of more than 10 patients on GKRS for central neurocytoma [6,15,14]. The largest study with 42 patients has been conducted by an international multicenter group [14]. In this series, the mean tumor volume was 12 cc and the mean PD was 14 Gy. Six of 42 (32%) patients developed ventricle enlargement requiring surgical intervention. Mortality was 0%, 1 patient died of unrelated causes. The 10-year tumor control rate was 81%.

Figure 8a shows the central neurocytoma WHO II in an asymptomatic 37-year old female patient which was treated by the author with GKRS. The tumor volume was 11.5 cc, the PD was 14 Gy to the 50% isodose and the tumor margin. At the 6.5-year FU, the tumor had regressed and the patient stayed asymptomatic (Figure 8b). GKRS seems to be a good alternative or supplement to open microsurgery or endoscopic surgery.

Figure 8a: Axial T2-weighted MRI showing a 11.5 cc neurocytoma WHO II in the third ventricle at the time of GKRS. The left parieto-occipital artifact is caused by the ventricular drainage and the intraventricular drain is seen next to the tumor.
**Subependymoma**

There are only 3 cases reported in two publications [2,17]. Figure 9a shows the paraventricular ependymoma WHO I in an asymptomatic 31-year old female patient which was treated by the author with GKRS. The tumor volume was 8.9 cc and the PD was 16 Gy to the 50% isodose and the tumor margin. At the 9-year FU, the tumor had regressed and the patient stayed asymptomatic throughout the entire FU period (Figure 9b).

**Figure 8b:** Axial T2-weighted MRI showing the tumor which has reduced in size more than 6 years after GKRS. The intraventricular drain is still in place.

**Figure 9a:** Axial T1-weighted MRI with contrast enhancement showing a 8.9 cc subependymoma WHO I in the third ventricle at the time of GKRS.
Metastases

Most probably, the majority of intraventricular metastases are treated by whole brain radiotherapy (WBRT) rather than GKRS since they are in direct contact with the cerebrospinal fluid (CSF) and may therefore spread within the CNS. That may be the reason why there are not many reports on GKRS for intraventricular metastases. There is one report by the Siomin V et al. who published a series of 16 patients undergoing GKRS for intraventricular metastases [34]. The primary malignancy was renal cell carcinoma in 14/16 (87.5%) patients. The mean tumor volume was 2.4 cc and the PD was 24 Gy to the 53% isodose and the tumor margin. The authors report no complications related to GKRS and no local treatment failures. Of the 16 patients, 12 (75%) died of systemic tumor disease and 2 (12.5%) of progressive multifocal metastatic CNS disease. In keeping with the excellent results of GKRS for CNS metastases in other locations, the results of GKRS for intraventricular metastases are promising. This may come as a surprise since intraventricular metastases bare the risk of CSF spread and GKRS is only a focal treatment. According to this study, direct contact of intraventricular metastases with CSF does not seem to heighten the risk of tumor spread substantially. For unknown reasons and unlike other tumors, renal cell carcinomas seem to have a preponderance to metastasize into the cerebral ventricles [31].

GAMMA KNIFE RADIOSURGERY FOR PINEAL LESIONS

The list of lesions of the pineal region is long and so is the list of pineal lesions which have been treated with GKRS: pineocytomas or pineal parenchymal tumors (PPT), pineoblastomas, astrocytomas, ependymomas, papillary epithelial tumors, and germ cell tumors [8,18,29,36,38].
For practical reasons, neoplastic lesions of the pineal region may be classified as germ cell tumors, non-germ cell tumors, and metastases. The largest series with 147 patients has been published by the Wentao L et al. [36]. The mean tumor volume was 8.5 cc and the PD was 13.6 Gy to the tumor margin. The overall local tumor control rate was 91% at 5 years following GKRS. The local tumor control rate for germ-cell tumors was 77% at 5 years following GKRS. Severe brain edema with raised intracranial pressure developed in 3/147 (2%) patients. All 3 had to be treated in the intensive care unit and 1/147 (0.6%) patient died due to intractable brain edema and subsequent brain herniation. The second largest series with 44 patients was published by the Yianni J et al. [38]. The mean tumor volume was 3.8 cc and the PD was 18.1 Gy to the tumor margin. Overall progression free survival (PFS) was 67% at 20 years following GKRS. Factors which were statistically significantly associated with worse outcome were: higher initial tumor grade, previous radiotherapy, and radiological evidence of necrosis. Five-year progression free survival was 47% for patients with those features versus 91% for patients without those features. The value of recommendations based on those publications is questionable. In select cases it may be reasonable to advocate GKRS for small low-grade parenchymal pineal tumors which haven’t undergone prior fractionated radiotherapy.

In general, the risks of GKRS for pineal lesions are high since radiation induced perifocal edema may lead to an acute occlusion of the aqueduct or to midbrain damage with devastating or even fatal consequences. This is what may have happened in the 2 published fatalities shortly after GKRS for pineal lesions [18,36]. GKRS is a focal therapy and is therefore of questionable value in higher-grade pineal tumors which are in direct contact with the CSF. Not surprisingly, leptomeningeal tumor spread seems to be a problem in those patients [8,18]. GKRS is not recommended as a first choice therapy for pineal lesions.

**GAMMA KNIFE RADIOSURGERY FOR LESIONS OF THE CAVERNOUS SINUS AND THE SELLATURCICA**

Undoubtedly, the cavernous sinus and the sella turcica are critical locations for any kind of lesion. The publication list of lesions of the cavernous sinus which have been treated with GKRS includes meningiomas, pituitary adenomas (PA), schwannomas, hemangiomas, and metastases. While meningiomas are rather common lesions of the cavernous sinus, schwannomas, hemangiomas, and metastases are not. Even though cavernous sinus meningiomas and PA of the cavernous sinus are rather common lesions, they are included in this section because otherwise the discussion of lesions in the cavernous sinus would be incomplete.

The list of lesions of the pituitary gland is long and not all the lesions which present as PA are necessarily PA [22,30]. The rate of unexpected histology in presumed endocrine inactive PA seems to be as high as 18% [22]. The publication list of lesions of the sella turcica which have been treated with GKRS includes PA, craniopharyngiomas, meningiomas, SFT, metastases, sarcomas, and even lymphocytic hypophysitis. Because of their anatomically critical location, lesions of
the cavernous sinus and the sella turcica may be considered “geographically” malignant lesions posing a special challenge to any neurosurgeon.

**Meningiomas of the Cavernous Sinus**

The five publications with series of 100 cases or more [13,28,32,35,37] are listed in Table 1. All five publications with a total of more than 1'300 patients show that GKRS for cavernous sinus meningiomas have excellent results compared to open microsurgery. In the two largest series which alone list more than 1'000 patients, the authors were able to show that recovery of pre-existing cranial nerve deficits was significantly better in patients who did not undergo prior surgery and in those who had smaller tumors [13,32]. In other words, improvement of cranial nerve deficits due to cavernous sinus meningioma is best if patients undergo GKRS as a sole and primary treatment. For obvious reasons, improvement of cranial nerve deficits in such situations also depends on the time which has elapsed since the onset of symptoms. Unfortunately, diplopia which is the most common presenting symptom in meningiomas of the cavernous sinus is sometimes misinterpreted leading to a delayed diagnosis. It is my personal impression that diplopia which has occurred as long as up to 3 months before GKRS usually resolves entirely. It is also my impression that if it resolves it usually resolves within a time frame of 6 weeks up to 3 months after GKRS.

Figure 10a shows a right cavernous sinus meningioma in a 69-year old female patient which was treated by the author with GKRS. Before GKRS, the patient underwent a transsphenoidal biopsy of the tumor by the author because she had been diagnosed with a non-Hodgkin lymphoma 14 years before. The transsphenoidal route was chosen since the tumor invaded the sphenoid sinus. Therefore this was the access with the least risk for the patient. The histology revealed a meningioma WHO I and the patient underwent GKRS 4 weeks later. The patient had a slight right oculomotor nerve deficit before the transsphenoidal biopsy and at the time of the GKRS. The tumor volume was 15.9 cc and the PD was 12 Gy to the 50% isodose and the tumor margin. Six months later, the cranial nerve deficit had resolved. Figure 10b shows the controlled tumor 6 years after GKRS. Once the right oculomotor nerve deficit had resolved, the patient remained asymptomatic throughout the 6-year FU period.
Table 1: Results of studies with 100 or more patients on GKRS for cavernous sinus meningiomas.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Tumor volume (cc)</th>
<th>PD (Gy)</th>
<th>Tumor control (5-y FU)</th>
<th>Tumor control (10-y FU)</th>
<th>Cranial nerve deficit new or worse</th>
<th>Cranial nerve deficit better</th>
<th>New pituitary insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeie GO et al. 2010</td>
<td>100</td>
<td>7.4</td>
<td>12.4</td>
<td>94%*</td>
<td>92%^</td>
<td>6%</td>
<td>21%</td>
<td>NA</td>
</tr>
<tr>
<td>Williams BJ et al. 2011</td>
<td>138</td>
<td>7.5</td>
<td>13.7</td>
<td>95%</td>
<td>71%</td>
<td>10%</td>
<td>NA</td>
<td>0%</td>
</tr>
<tr>
<td>Kano H et al. 2013</td>
<td>272</td>
<td>7.9</td>
<td>13</td>
<td>94%</td>
<td>86%</td>
<td>11%</td>
<td>14% prior surgery</td>
<td>37% no surgery</td>
</tr>
<tr>
<td>Pollock BE et al. 2013</td>
<td>115</td>
<td>9.3</td>
<td>16</td>
<td>99%</td>
<td>93%</td>
<td>10%</td>
<td>41%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sheehan JP et al. 2014</td>
<td>763</td>
<td>8.8</td>
<td>13.2</td>
<td>95%</td>
<td>82%</td>
<td>9.6%</td>
<td>34%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

GKRS = Gamma Knife Radiosurgery, PD = Prescription Dose, FU = Follow-Up, NA = Not Applicable, * = Excluding patients with atypical meningiomas.

Results of studies with 100 or more patients on GKRS for cavernous sinus meningiomas. The study of Skeie GO et al. [35] includes atypical meningiomas. This study's tumor control rates are 94% and 92% at the 5-year and 10-year follow-up if atypical meningiomas are excluded from the evaluation. Kano H et al. [13] demonstrate that prior surgery significantly decreases the chance of recovery of cranial nerve deficits after GKRS (p=0.001).

Figure 10a: Axial T1-weighted MRI with contrast enhancement showing a 15.9 cc meningioma of the right cavernous sinus at the time of GKRS. Extracranially, the fiducials for the GKRS are visible as 3 artifacts on each side.
Schwannomas and Hemangiomas of the Cavernous Sinus

There is one publication by Hayashi M et al. listing several benign tumors of the cavernous sinus besides meningiomas and PA: 6 schwannomas, and 6 hemangiomas [10]. Schwannomas and hemangiomas were treated with a PD of 12 Gy. The results for hemangiomas are good with a tumor control rate of 100% and no morbidity. For schwannomas, the authors report a tumor control rate of 100% but cranial nerve deficits in 83% of the patients. Typically, schwannomas react to radiosurgery with a transient tumor expansion which peaks at about 6 months following GKRS and may last up to 18 months [24]. Unlike VS, schwannomas of the cavernous sinus are located within a confined space surrounded by dura mater and bone. A transient tumor expansion may therefore lead to raised pressure within the cavernous sinus compressing cranial nerves. In one case, the authors report on cyst formation of a schwannoma after GKRS causing cranial nerve deficits.

Because of their unique response to radiosurgery, schwannomas of the cavernous sinus may not be the best candidates for GKRS.

Metastases of the Cavernous Sinus and the Sellaturcica

There are 3 publications [11,12,26] with small series of metastases in the cavernous sinus. Mori Y et al. [26] include metastases to the pituitary gland and they introduce a classification of metastases to the cavernous sinus region based on the invasion of various anatomical structures.
This classification is important for radiosurgery because dose may vary for the different locations which in turn may have an effect on prognosis. Mori Y et al. differentiate between metastases to the pituitary gland only (Type 1), to the cavernous sinus only (Type 2), and to both the cavernous sinus and the sella turcica (Type 3). The overall median tumor volume in their series with a total of 13 patients was 3.4 cc. The median PD was 12 Gy for Type 1 tumors and it was 16 Gy for Types 2 & 3 tumors. Local tumor control was achieved in 89% (Table 2).

Table 2: Proposal for a modified Mori-classification of metastases in the cavernous sinus region.

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Patients (n)</th>
<th>PD (Gy)</th>
<th>Complete response (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pituitary gland only</td>
<td>4</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cavernous sinus only</td>
<td>5</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Cavernous sinus &amp; sella turcica</td>
<td>4</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cavernous sinus &amp; sphenoid sinus</td>
<td>1</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

PD = Prescription Dose

The tumor Types 1, 2, & 3 are patients of Mori’s publication (Mori) and the tumor Type 4 patient is the author’s own patient (Figures 9a & b). The definition of complete response is disappearance of the tumor following GKRS. Treatment response was best for tumor Types 2 & 4.

Figure 11a shows a right cavernous sinus metastasis in a 59-year old female patient 3 months after bilateral mastectomy for a multicentric lobular invasive breast cancer. At that time, the patient was asymptomatic. The tumor was treated by the author with GKRS. The tumor volume was 4.4 cc and the PD was 20 Gy to the 50% isodose and the tumor margin. Figure 10b shows the 9-year FU with no indication of tumor recurrence. The patient remained asymptomatic throughout the 9-year FU period and developed no further intracranial metastases.

Figure 11a: Coronal T1-weighted MRI with contrast enhancement showing a 4.4 cc metastasis in the right cavernous sinus and the sphenoid sinus at the time of GKRS.
The author’s own case (Figures 11a & b) involves the cavernous sinus and the sphenoid sinus only. This tumor location is not covered by the Mori classification and therefore requires a modification of that classification. The author proposes to classify such tumors as Type 4 tumors. This distinction is relevant for radiosurgery because Type 4 metastases may be treated with a PD comparable to Types 2 & 3 tumors which is significantly higher than the PD which may be applied to Type 1 tumors (see Table 2). In addition, this modified classification is important for prognosis. Complete response or disappearance of the tumor was only achieved in Type 2 metastases (Mori) and the author’s own patient with a Type 4 metastasis (Figure 11b). One may speculate that Type 4 tumors may respond just as favorable to GKRS as Type 2 tumors (Table 2).

**Benign Lesions of the Sellar Turcica**

PA and craniopharyngiomas are the most common lesion of the sella turcica to be treated with GKRS. The literature is abundant on GKRS for residual or recurrent tumor following open microsurgery. Accordingly, an in-depth discussion of GKRS for these tumors cannot be part of this chapter on uncommon lesions in critical locations. PA and craniopharyngiomas are complex tumors by themselves and deserve to be discussed in chapters of their own.

**Gamma Knife Radiosurgery for Cranial Nerve Lesions**

The typical pathologies are different for the various CN. The olfactory nerve is most often affected by meningiomas of the olfactory groove, the optic nerve by periophthalmic meningiomas, and the auditory nerve by schwannomas. Periophthalmic- or skull base meningiomas are common lesions and the literature on GKRS for skull base meningiomas is exhaustive. Therefore, the discussion of GKRS for periophthalmic meningiomas is not part of this chapter on uncommon lesions in critical locations. VS are by far the most common CN lesion and there is extensive
literature on GKRS for acoustic neuromas. Therefore, the discussion of GKRS for VS cannot be part of this chapter either. On the other hand, schwannomas of other cranial nerves are rare and the involvement of cranial nerves makes their location critical.

**Cranial Nerve Schwannomas**

The studies with more than 30 patients [4,9,33] are listed in Table 3. Tumor control rates are excellent, new or worsened neurological deficits developed in about 12% of the patients. Transient tumor expansion following GKRS which is typical for schwannomas was the only factor associated with worsening of facial nerve function [9].

**Table 3:** Results of studies with more than 30 patients on GKRS for non-vestibular cranial nerve schwannomas.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cranial nerve (n)</th>
<th>Patients (n)</th>
<th>Tumor volume (cc)</th>
<th>PD (Gy)</th>
<th>Tumor control</th>
<th>New or worsened deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharkawy M et al. 2012</td>
<td>Trigeminal N, 25</td>
<td>36</td>
<td>2.9</td>
<td>13.5</td>
<td>81%</td>
<td>11%</td>
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<tr>
<td></td>
<td>Hypoglossal N, 3</td>
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<td></td>
<td>Abducent N, 2</td>
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<tr>
<td></td>
<td>Jugular foramen, 2</td>
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<tr>
<td></td>
<td>Facial N, 1</td>
<td></td>
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<tr>
<td></td>
<td>Trochlear N, 1</td>
<td></td>
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<tr>
<td></td>
<td>Oculomotor N, 1</td>
<td></td>
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<tr>
<td></td>
<td>Glossopharyngeal N, 1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hasegawa T et al. 2015</td>
<td>Facial N</td>
<td>42</td>
<td>2.5</td>
<td>12</td>
<td>92% (5-year FU)</td>
<td>12%</td>
</tr>
<tr>
<td>Sheehan JP et al. 2015</td>
<td>Facial N</td>
<td>42</td>
<td>1.8</td>
<td>12.5</td>
<td>90% (5-year FU)</td>
<td>12%</td>
</tr>
</tbody>
</table>

**PD** = Prescription Dose, **N** = Nerve, **FU** = Follow-Up

Results of Gamma Knife radiosurgery for non-vestibular schwannomas.

Figure 12a shows a left facial nerve schwannoma in a 41-year old male patient. The patient had a 1-year history of some degree of a left-sided hearing loss. The tumor had been biopsied 4 months prior to GKRS and the histological diagnosis confirmed a schwannoma. According to the classification of Hasegawa T [9], the tumor was a Type IV facial nerve schwannoma. The tumor was treated by the author with GKRS. The tumor volume was 1.7 cc at the time of GKRS and the PD was 13 Gy to the 50% isodose and the tumor margin. Figure 12b shows the shrunken tumor 11 years after GKRS. Serviceable hearing on the left side was preserved throughout the 11-year FU and the patient never developed any facial nerve deficit.
**Figure 12a:** Axial T1-weighted MRI with contrast enhancement showing a 1.7 cc left facial nerve schwannoma at the time of GKRS.

**Figure 12b:** Axial T1-weighted MRI with contrast enhancement showing the reduced tumor volume 11 years after GKRS.
Figure 13a shows a right trigeminal nerve schwannoma in a 49-year old female patient. The patient had a several-year history of dysesthesia of the first branch of the right trigeminal nerve without any neurological deficit. The tumor was treated by the author with GKRS. The tumor volume was 2.6 cc at the time of GKRS and the PD was 14 Gy to the 50% isodose and the tumor margin. Figure 13b shows the shrunken tumor 15 years after GKRS. Apart from an intermittent slight dysesthesia of the second branch of the right trigeminal nerve, the patient remained asymptomatic throughout the 15-year FU.

Figure 13a: Axial T1-weighted MRI with contrast enhancement showing the 2.6 cc right trigeminal nerve schwannoma at the time of GKRS.
Figure 13b: Axial T1-weighted MRI with contrast enhancement showing the reduced tumor volume 15 years after GKRS. The tumor developed a hypo intense center which remained unchanged throughout the FU.

Meningiomas of the Olfactory Groove

Gande A et al. have published 41 patients who underwent GKRS for olfactory groove meningiomas [5]. The median tumor volume was 8.5 cc, the median PD was 13 Gy to the tumor margin, and the estimated median dose to the olfactory nerve was 5.1 Gy. The tumor control rate was 95% at 20 years. Subjective intact olfaction was reported in 66% of the patients, partial anosmia in 22%, and complete anosmia in 12%. Return to intact olfaction following GKRS was described by 7% of the patients. GKRS for olfactory groove meningiomas is an excellent alternative to open microsurgery.

Figure 14a shows an olfactory groove meningioma in an asymptomatic 63-year old female patient. An MRI was done because the patient had a short lasting episode of amnesia one month before. The tumor was treated by the author with GKRS. The tumor volume was 2.4 cc and the PD was 15 Gy to the 50% isodose and the tumor margin. Figure 14b shows the shrunken tumor at the 9-year FU. The patient remained asymptomatic throughout the entire FU period and had no further amnestic episodes. Her subjective olfaction was still intact 9 years after the GKRS.
CONCLUSION

GKRS is safe and effective for most lesions in uncommon and critical locations. Primary GKRS seems to be the best treatment choice in most of those cases. If the lesions are diagnosed at an early stage before they lead to neurological deficits, such deficits may be avoided altogether. If they are diagnosed when they lead to incipient neurological deficits, such deficits may very well resolve following GKRS. This is especially true for cranial nerve schwannomas, for intraventricular lesions, for benign tumors of the skull base and for AVMs or metastases within or in close proximity to eloquent cortex.
References


