Gamma Knife Radiosurgery

A Review of Epidemiology and Clinical Practice

2020

LEKSELL
GAMMA KNIFE
SOCIETY

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Introduction

This report represents a summary of conditions managed using Leksell Gamma Knife Stereotactic Radiosurgery (GKRS). Since the publication of the first report in 1967, thousands of articles have been published presenting both short- and long-term outcomes of a variety of diseases managed using GKRS. The range of pathologies extends from functional disorders, to life threatening malignant and vascular intracranial lesions. This report will present an update on the current uses, epidemiology and outcome data pertaining to the use of GKRS.

The following are some of the factors studied by epidemiology:
1. The study of the course, or natural history, of diseases
2. The frequency of diseases in populations
3. The patterns of disease occurrence
4. Risk factors for and potential causes of disease
5. The effectiveness of preventative and treatment measures

The following are considered in estimating the number of indications suitable for treatment with Gamma Knife Radiosurgery:
1. The incidence of a relevant disease in a population. *–How many new cases a year are suitable for GKRS?*
2. The prevalence of a relevant disease. *–What is the total number of cases in each population?*

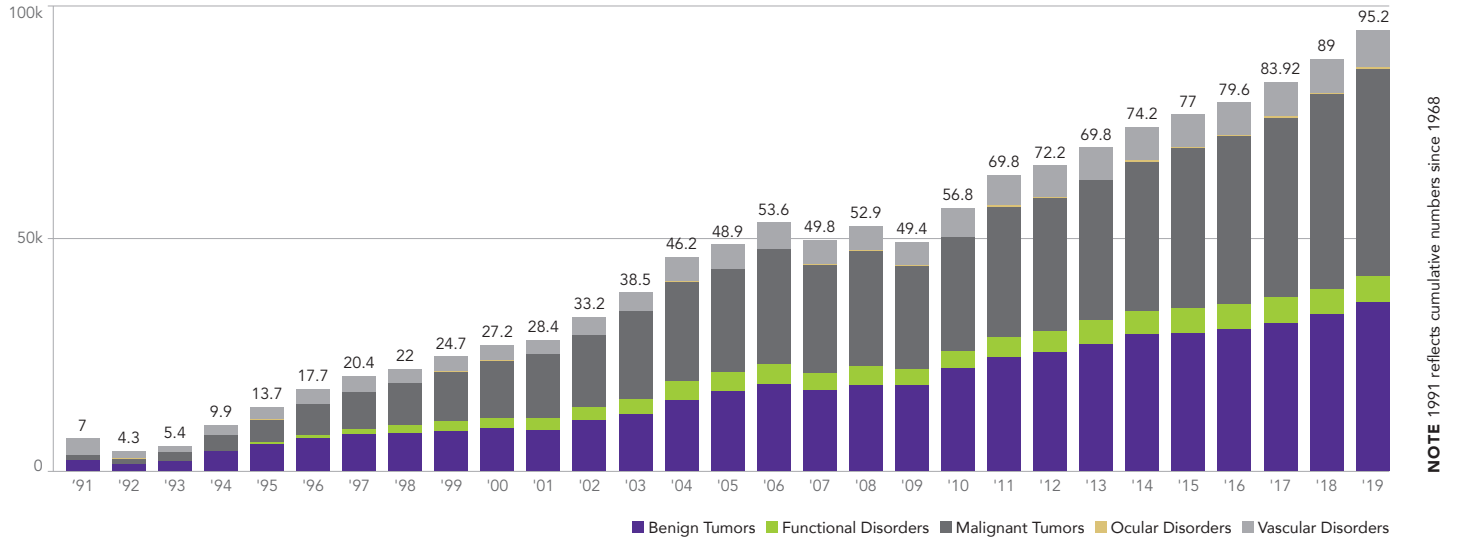**Estimations of the role of GKRS are not always easy because:**
1. Epidemiological studies are set up to examine a given disease.
2. GKRS is appropriate for a subset of the total number of patients.
3. The indications for GKRS are increasing because of advances in imaging and the GKRS technology itself. In most societies, structural brain issues such as tumors and vascular malformations are recognized at earlier stages because of the widespread availability of MRI. However, earlier recognition does not always mean that GKRS or any other treatment option is required, since indications vary related to volume, anatomic location, age of the patient, symptoms or signs present at the time of diagnosis, and risks of more invasive options. The natural history of some tumors is such that in some patients no intervention is needed.
4. The incidence of disease in a given population may vary widely depending on the geographical area and the socioeconomic status of that area.

A reasonable estimation of the number of cases treatable by Gamma Knife are provided in the Summary Table on the following page. However, tables reporting the average number of cases treated each year at certain Gamma Knife centers is provided on pages 19–21 using data from centers in North America, Europe and Asia. Data from such high-volume centers is dependent on the referral patterns to those specific institutions and may not reflect the effect of the increasing number of GKRS units in these geographical areas. ●
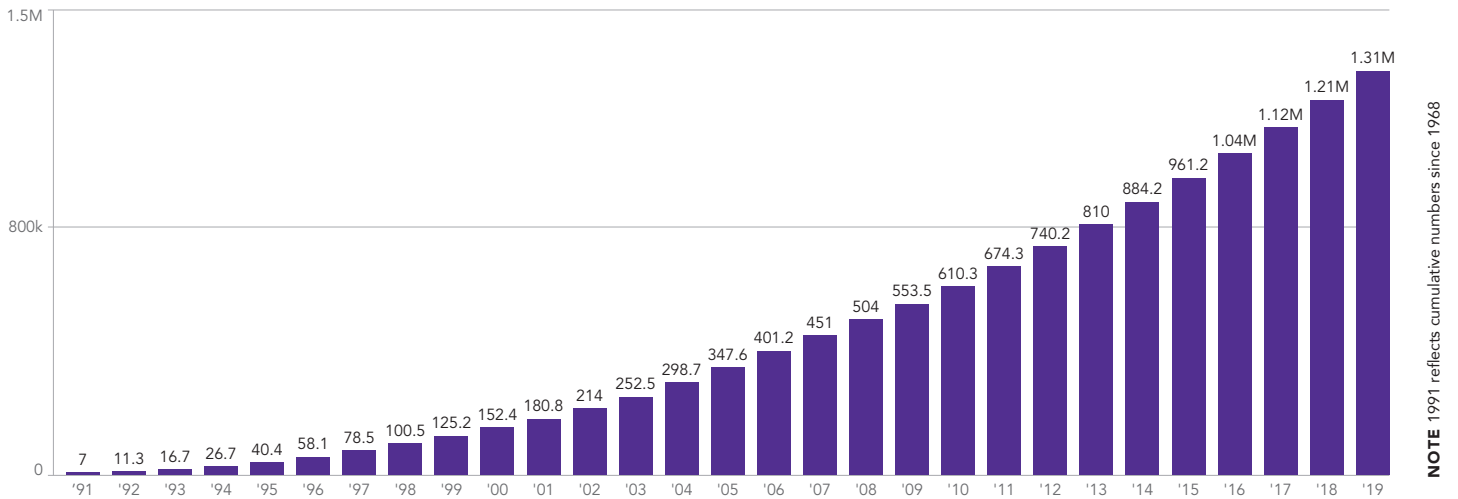
SUMMARY OF NEUROLOGICAL DISORDERS TREATABLE WITH LEKSELL GAMMA KNIFE

		Annual Incidence (per million)	% indicated for Gamma Knife treatment	Annual Gamma Knife cases (per million)
Vascular Malformations	Arteriovenous Malformations	8.9–13.4 [1–3]	70	6.2–9.4
	Cavernous Malformations	1.5–5.6 [4]	15	0.2–0.84
	Dural Arteriovenous Fistulas	1.7 [5]	50	0.85
Functional Disorders	Trigeminal Neuralgia	126–289 [6–7]	50	63–144.5
	Essential Tremor	237 [8]	50	118.5
	Parkinson's Tremor	200 [9]	15	30
	Epilepsy	610 [10]	5	30.5
Benign Tumors	Meningioma	86 [11]	50	43
	Pituitary Adenoma	40.1 [11]	15	6
	Vestibular Schwannoma	20 [11]	80	16
	Craniopharyngioma	1.3 [12]	20	0.26
Malignant Tumors	Metastases	300–500 [13–14]	90	270–450
	Glioblastoma Multiforme	32 [11]	20	6.4
	Anaplastic Astrocytoma	5.9 [11]	20	1.1
	Diffuse Astrocytoma	4.6 [11]	20	0.9
	Lymphoma	4.3 [11]	10	0.43
	Uveal Melanoma	5.1 [15]	40	2.04
TOTAL				**595–861**

INDICATIONS TREATED ANNUALLY WITH LEKSELL GAMMA KNIFE THROUGH 2019 WORLDWIDE

Values by year ('91–'19): 7, 4.3, 5.4, 9.9, 13.7, 17.7, 20.4, 22, 24.7, 27.2, 28.4, 33.2, 38.5, 46.2, 48.9, 53.6, 49.8, 52.9, 49.4, 56.8, 69.8, 72.2, 69.8, 74.2, 77, 79.6, 83.92, 89, 95.2

Legend: ■ Benign Tumors ■ Functional Disorders ■ Malignant Tumors ■ Ocular Disorders ■ Vascular Disorders

NOTE 1991 reflects cumulative numbers since 1968

OVER 1.3 MILLION PATIENTS TREATED WITH LEKSELL GAMMA KNIFE THROUGH 2019 WORLDWIDE

Values by year ('91–'19): 7, 11.3, 16.7, 26.7, 40.4, 58.1, 78.5, 100.5, 125.2, 152.4, 180.8, 214, 252.5, 298.7, 347.6, 401.2, 451, 504, 553.5, 610.3, 674.3, 740.2, 810, 884.2, 961.2, 1.04M, 1.12M, 1.21M, 1.31M

NOTE 1991 reflects cumulative numbers since 1968

Vascular Abnormalities

Arteriovenous Malformations

Brain arteriovenous malformation (AVM) is a congenital vascular anomaly consisting of an abnormal collection of arteries and veins connected by an intervening nidus. AVMs are rare, with an estimated incidence ranging between 0.89 to 1.34 cases per 100,000 and a prevalence estimated at 18 per 100,000. [1–3]

In the absence of treatment, the overall risk of spontaneous hemorrhage is estimated to range from to 2% to 5% per year. [16–17] Moreover, the risk of re-hemorrhage is significantly higher in patients with prior bleeds, with reported early re-bleed rates ranging from 6% to 18% per year. [17–18]

More than 50% of individuals with AVMs present with hemorrhage, most commonly an intraparenchymal hemorrhage or a subarachnoid hemorrhage. [19] Estimates on the overall risk of spontaneous AVM hemorrhage vary, but typically range from around 2–4% per year and possibly less for unruptured AVMs. [16 20–26] After an initial hemorrhage, the risk of re-bleeding is increased and ranges between 6–15% during the first year. [27–30]

Four options are available for the management of AVM; observation, surgical resection, radiosurgery, and embolization. The last 3 of which can be used alone or in combination. Multiple factors are considered when determining the best treatment option including age, presence of comorbidities, location and size of AVM, hemorrhage, the angioarchitecture of the AVM, and the presence of pre or intranidal aneurysms.

The role of observation in patients with unruptured AVM was brought into sharper focus after the publication of the findings of the ARUBA trial. [31] In the study, 109 patients were randomized to medical management, while 114 were assigned to receive intervention, either embolization, SRS, microsurgery, or a combination thereof. The primary outcome measures were the occurrence of stroke or death. During a follow-up period of 33 months, 30.7% of the patients undergoing intervention suffered a stroke or died, compared to only 10.1% in the medical management arm. Three times as many patients in the intervention cohort were clinically impaired (modified Rankin score of two or higher), 46.2% versus 15.1%. The population were followed for less than three years and the authors concluded that medical management was superior to medical management plus intervention for unruptured AVMs. The findings of this report were extensively criticized, particularly regarding use of embolization in most patients, and the short follow up period. In fact, Karlsson et al. collected data from 1,351 patients treated with GKRS for unruptured and untreated AVMs, and found the incidence of stroke after 5 years was significantly less in the intervention group, owing to the higher rates of complete obliteration as length of follow up increases. [32] Ding et al. published a multicenter report on the outcomes of GKRS for ARUBA eligible Spetzler-Martin grades I and II AVM. The findings pointed to highly favorable outcomes of GKRS compared to the natural history. [33] Using the same eligibility criteria as the ARUBA trial, Pollock et al. retrospectively observed that the risk of stroke or death in 174 patients treated by SRS was 2% per year for the first five years after treatment, and 0.2% thereafter. [34] They suggest that patients harboring small volume AVMs may benefit from SRS when compared to the natural history over a period of 5–10 years.

Radiosurgery causes AVM obliteration by inducing vascular injury and fibrosis that eventually leads to vessel thrombosis and occlusion. [35] AVM obliteration rates vary widely and depend on the radiation dose administered and the volume of the AVM. The primary advantage of SRS for AVMs is surgical risk avoidance, while the chief limitation is the latency period from the time of treatment to obliteration during which the risks of hemorrhage persists. This latency period is typically around two to four years but can be longer. Patients who are not candidates for microsurgery due to advanced age, medical comorbidities, and surgical inaccessibility are often eligible for treatment with SRS. A complication unique to SRS treatment of AVMs is an adverse radiation effect (ARE).

VASCULAR DISORDERS – ACCUMULATED NUMBERS TREATED WORLDWIDE 1968–2019

NOTE 1991 reflects cumulative numbers since 1968
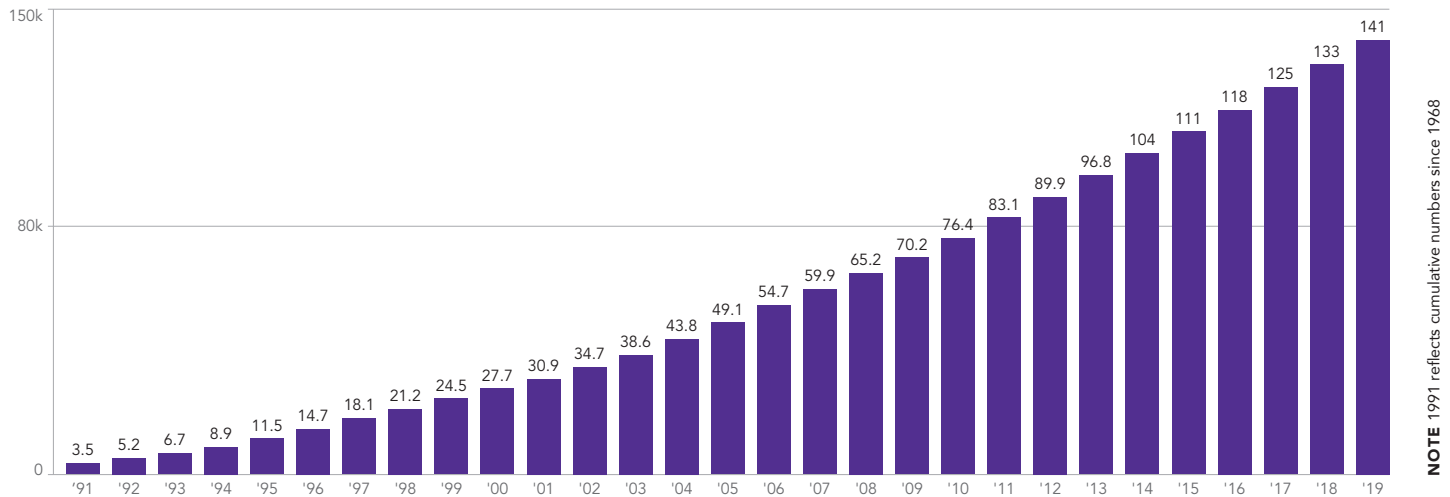
GKRS is primarily used for deep seated Spetzler-Martin grade I–III lesions. More recently, large volume AVM (>10cc) have been treated by GKRS using a volume staged approach during which separate components of the nidus are treated over multiple procedures to expose the nidus at a therapeutic dose and minimize radiation exposure to nearby structures. When the margin dose is ≥ 17 Gy and the 20 Gy SRS volume included ≥ 63% of the total target volume, the angiographically confirmed obliteration rates increased to 61% at 5 years and 70% at 10 years. [36]
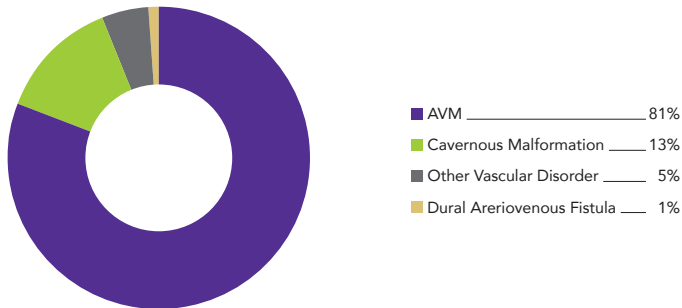
A report from Linköping, Sweden takes advantage of Scandinavia's stable population and excellent health care documentation. This report was a prospective study of nearly 1,000,000 patients over a 10-year period. The importance of this study is that it was prospective, and nobody was lost to follow-up. From the point of view of GKRS, the great majority of the patients (84.5%) of the AVMs were Spetzler-Martin Grades I–III. These are the lesions suitable for GKRS. Current knowledge indicates that approximately 10 cases per million AVMs are suitable for GKRS. With the current advancements in imaging, combined with the use of volume staging in the management of larger AVMs, the number of adult and pediatric patients undergoing GKRS is expected to increase as care moves more towards minimally invasive treatment options. **TABLE 1** presents the number of AVM patients treated per year at different centers.

Cavernous Malformations

Intracranial cavernous malformations (CM) can be detected incidentally on MRI or can be detected after a patient presents with a neurological deficit after a microhemorrhage. There is no male or female genetic predisposition. CM can arise sporadically, or in some cases can be familial. Additionally, patients with a prior history of whole brain radiation therapy will often have multiple incidental CM on MRI. Surveys suggest that CM is present in 0.5% of the population. [37] However, it tends to become symptomatic in only 40% of the cases. The bleeding impact is related to the location of the lesion. These lesions are often resected, particularly when they are in an easily accessible subcortical area. However, resection of lesions located in or near critical structures such as the brain stem or thalamus is often associated with a considerable risk of morbidity and mortality. [38]

The annual risk of a CM bleeding event is approximately 0.5% per year in patients whose CM has been found incidentally on imaging and has never bled. Most studies show that a new bleed rate increases to 1–4% per year after an initial hemorrhage. A small group of such patients have multiple bleeding events. After two or more bleeds, the annual bleeding risk increases to as high as 33% each year. For patients with subcortical lesions associated with epilepsy,

■ AVM _____ 81%
■ Cavernous Malformation _____ 13%
■ Other Vascular Disorder _____ 5%
■ Dural Areriovenous Fistula ___ 1%

surgical resection is considered. Most CM are observed until rebleeding events are confirmed. In patients with deep seated lesions not located on a cortical, pial, or ependymal surface, GKRS can be used. Treatment reduces the repeated hemorrhage risk to less than 1% per year after the initial two-year latency interval after radiosurgery. GKRS is performed with MRI localization and the target lies within the hemosiderin rim defined by MRI. A recently published report from the University of Pittsburgh Medical Center presented the outcomes of 76 patients with brain stem CM treated with GKRS. They reported an annual hemorrhage rate of 33% in patients who had more than 1 bleed, which after treatment with GKRS, was reduced to an annual hemorrhage rate of 4%. [39] **TABLE 2** presents patients with CM treated with GKRS at different centers.

Dural Arteriovenous Fistulas

The incidence of dural arteriovenous fistulas (DAVFs) has been estimated at 5–20% of all intracranial vascular malformations. [40] They are thought to be acquired due to inflammation, thrombosis, or trauma of the dural sinus. In some, however, DAVFs are considered idiopathic. Patients with spontaneous development of DAVFs, or those that develop after prior venous outflow thrombosis, require intervention if the fistula is associated with cortical venous drainage,

intractable pulsatile tinnitus, or severe ocular proptosis, pain and chemosis (in the case of a DAVF of the cavernous sinus). Many such patients are treated in conjunction with post radiosurgery DAVF embolization in order to achieve both early clinical response (embolization) and maintenance of long-term occlusion (radiosurgery). A recent meta-analysis of 19 reports comprising 729 patients with 743 DAVFs reported an obliteration rate of 63% with GKRS. [41] ●

Benign Tumors

Schwannomas

Vestibular Schwannomas (Acoustic Neuromas)

Vestibular schwannomas (VS) are most often benign tumors that arise from the vestibular portion of the vestibulocochlear nerve. They are the most common type of intracranial schwannomas. Most cases are sporadic, but some are associated with neurofibromatosis type II. Traditionally the incidence of VS has been thought to be 1 per 100,000, however, with advanced imaging techniques, VS are being detected when the tumor volume is smaller. An article published by Stangerup et al. in 2012, summarized the natural history and epidemiology of these tumors, and suggested that the incidence of VS peaked in 2004 at an estimate of 24 VS/million/year. [42] Since then, there has been a slight decrease and stabilization in the identification of new cases found to be at a rate of 19 VS/million/year by the end of 2008. The sudden increase since 1976 and stabilization of incidences by 2008 has been attributed to the improvement of diagnostic equipment, increased access to healthcare, and awareness of the general population. A review article by Schmidt et al. published in 2012 suggested that estimates of the prevalence of incidental VS (as verified by MRI in non-symptomatic patients) is 0.02% of the general population. The article compared the prevalence rates of two major articles published in 2000 and 2005. The former study examined patients with VS symptomology and proposed a prevalence of 0.07%. The statistical differences are believed to be attributed to the number and duration of MRI studies and inclusion/exclusion criteria for VS symptoms. [43–44] The most recent reports estimate the incidence of VS to be closer to 2 per 100,000. [11]

Since approximately 75% of VS patients are treatable by GKRS and using an incidence of 20 patients per million, we can estimate that approximately 15 patients per million inhabitants are candidates for Gamma Knife surgery.

Management of VS continues to generate some controversy. One of the reasons for this is the improved surgical results during the microsurgical era. Total tumor removal plus cranial nerve preservation, without additional complications remains an important goal. Publications from busy centers of excellence suggest that the results of surgical removal have significantly improved over the last 20 years. During the last 25 years GKRS has also become a frequently applied intervention, with more than 125,000 patients worldwide who have undergone this non-invasive treatment option. Since facial neuropathy has been virtually eliminated and hearing preservation rates may approximate 50–70% of patients after GKRS, the controversy related to the use of radiosurgery has largely abated. Controversy still exists about the timing of intervention and the relative benefit of early SRS for newly diagnosed patients vs. watchful waiting. Tumor growth rates under observation are estimated at 1–2 mm per year, although tumor volume doubling times have been suggested as 2.3 years. GKRS can be used as a primary treatment option for small to medium sized tumors, and as an adjuvant option when initial surgery is required for tumor debulking to relief mass effect. A report by Johnson et al. presented the long-term outcomes of 871 patients with VS who underwent GKRS. The tumor control rate was 94% at 10 years. [45] Cystic tumors often respond well to GKRS, compared to solid tumors. [46]

Over time, multiple reports evaluated specific patient and treatment parameters that influenced serviceable hearing preservation rates. These included age at the time of GKRS, the level of hearing at the time of treatment (Gardner-Robertson (GR) grade), and tumor volume. The authors presented the Pittsburgh Hearing Prediction Score (PHPS), which assigns a total of 5 points based on patient age (1 point if < 45 years, 2 points if 45–59 years, and 3 points if ≥ 60 years), tumor volume (0 points if < 1.2 cm^3, 1 point if ≥ 1.2 cm^3), and GR grade (0 points if grade 1 hearing, 1 point if grade 2 hearing). The serviceable hearing preservation rate was 92.3% at 10 years in patients whose score total was 1. In contrast, none of the patients whose PHPS was 5 maintained serviceable hearing at 10 years. [47] Other factors found to affect hearing outcomes include the timing of intervention (within 2 years of diagnosis), and minimizing the cochlear dose to less than 4.2 Gy. **TABLE 3** presents the number of patients treated at the major Gamma Knife centers.

Non-vestibular Schwannomas

Non-vestibular schwannomas (NVS) account for less than 10% of all intracranial schwannomas, and less than 0.5% of all intracranial tumors. [48] Symptoms secondary to these tumors are often related to either the dysfunction of the nerve of origin or due to the mass effect on the surrounding structures.

Trigeminal schwannomas (TS) are the second most common intracranial schwannomas, and they account for up to 0.3% of intracranial tumors, and 8% of intracranial schwannomas. [49] Trigeminal nerve dysfunction resulting in facial pain or numbness is the most common manifestation of this tumor. [50] Jugular foramen schwannomas (JFS) refer to tumors arising from Schwann cells covering the 9th, 10th, or 11th cranial nerves around the jugular foramen. They comprise around 3–4% of all intracranial schwannomas. [51–52] The most common symptoms of JFS are swallowing dysfunction, hoarseness and hearing loss. [53] Less common schwannomas of cranial nerves III, IV and VI can also be treated using GKRS.

Three treatment options are usually considered for the management of these tumors: surveillance with serial imaging, surgical resection and GKRS. [50 52 54–57] Reports on the natural history of these tumors are lacking, however, it is still considered reasonable to observe these tumors with serial imaging if they are discovered incidentally and are asymptomatic. [57]

Surgical resection has been the standard treatment option for NVS. Resection is often indicated when there is a symptomatic mass effect, or when there is diagnostic uncertainty. Complete tumor resection is often curative. However, despite the advances of skull base surgery, surgery remains associated with higher rates of morbidity, particularly with lower cranial nerve schwannomas. [55 58]

SRS provides an effective and non-invasive tool in the primary or adjuvant management of skull base neoplasms. SRS have been shown to achieve high tumor control and low complication rates. [59–60]

- Meningioma ——————— 40%
- Vestibular Schwannoma ——— 26%
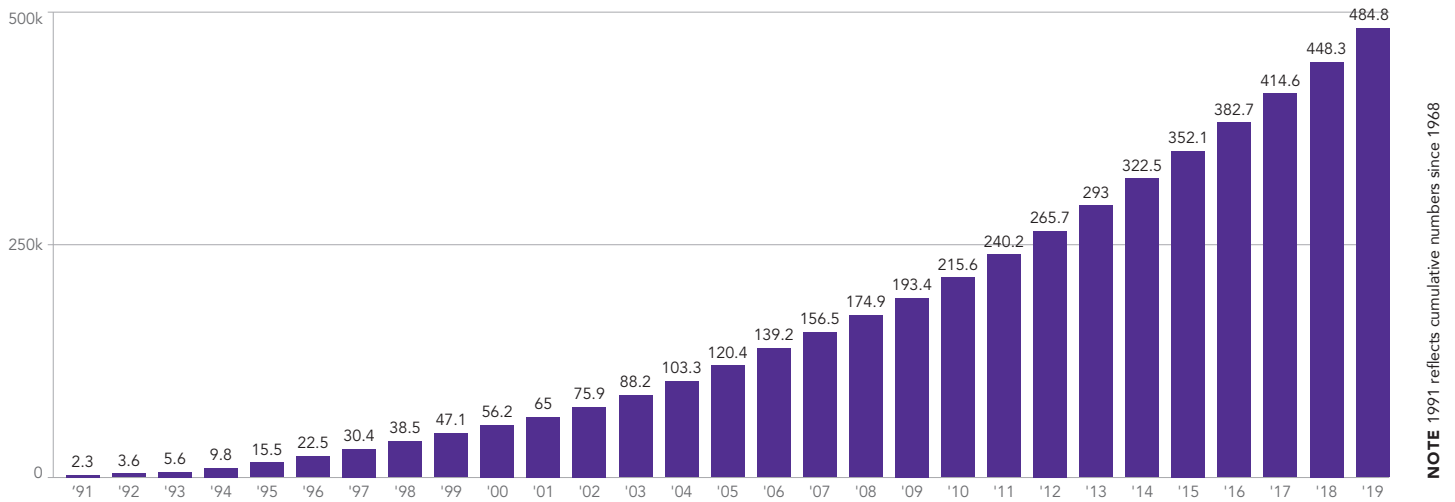- Pituitary Adenoma ————— 18%
- Other Benign Tumors ———— 18%
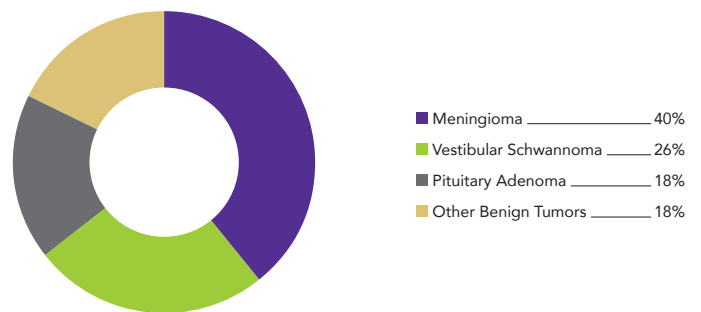
Meningiomas

Meningiomas are the most common benign intracranial tumors. The incidence of meningiomas is estimated to be 8.6 per 100,000. Of the histologically identified meningiomas diagnosed between 2013 and 2016 in the United States, 79.3% were classified as WHO grade I, 17.7% as grade II, and 1.7% as grade III. [11]

The median age at the time of diagnosis is 66 years. The central Brain Tumor Registry of the United States estimates that there will be approximately 34,210 new meningioma cases in the United States in the year 2020. [11]

Anatomically located skull base meningiomas are often suitable for GKRS because of the higher incidence of surgical complications after microsurgery for many skull base meningiomas. Convexity or falcine meningiomas may be suitable for GKRS as well, but most patients with symptomatic larger tumors generally are considered for craniotomy and resection as the first line option in patients eligible for general anesthesia and resection. The ratio of non-basal to basal meningiomas is 2.3/1. This would give an incidence based on the Central Brain Tumor Registry of the United States (CBTRUS-2013) of 32 per million per year where

500k

250k

0

2.3 '91
3.6 '92
5.6 '93
9.8 '94
15.5 '95
22.5 '96
30.4 '97
38.5 '98
47.1 '99
56.2 '00
65 '01
75.9 '02
88.2 '03
103.3 '04
120.4 '05
139.2 '06
156.5 '07
174.9 '08
193.4 '09
215.6 '10
240.2 '11
265.7 '12
293 '13
322.5 '14
352.1 '15
382.7 '16
414.6 '17
448.3 '18
484.8 '19

NOTE 1991 reflects cumulative numbers since 1968

GKRS may be a first line management option. In addition, treatable non-basal meningiomas include residual or recurrent tumors after initial attempted resection. Depending on patient age, presentation, and symptoms or signs, some patients with basal meningiomas warrant observation until symptoms develop or repeat imaging defines additional tumor growth. The total number of meningioma patients for whom GKRS may be indicated varies from 33–88 per million per year. **TABLE 4** presents a summary of reports on meningiomas treated with GKRS.

Pituitary Tumors

The most recent epidemiological series report the incidence of pituitary tumors as 4.08 per 100,000. [11] Prior autopsy studies have shown that up to 30% of normal patients may have incidental pituitary lesions (including adenomas, Rathkes cleft cysts, craniopharyngiomas). A report from Finland gives a documented incidence of approximately 40 patients per million. It is estimated that 14,120 patients with pituitary tumors will be diagnosed in 2020. [7]

To understand these tumors properly, they must be considered as two types. Patients with larger tumors that compress adjacent structures, such as the optic chiasm or extend laterally into the cavernous sinus, usually require initial surgery. Most such tumors are not endocrine active but may lead to gradual pituitary hormone loss as the tumor damages normal gland function. Some pituitary tumors are endocrine active and produce an excess of a specific hormone that may impact quality and length of life if left untreated. There are three most commonly recognized endocrine active pituitary tumors: prolactinomas (making excess prolactin – PRL), growth hormone – GH secreting tumors that lead to clinical acromegaly, and ACTH producing tumors that lead to Cushing's disease, a condition that reflects the excess ACTH production leading to hypercortisolism caused by excess steroid production by the adrenal glands. PRL affects menstruation and fertility in women and potency in men.

A macroadenoma is a tumor that has a maximum diameter of 2 cm or more. A tumor smaller than 1 cm diameter is a microadenoma. Endocrine active tumors require treatment

to correct the hormone abnormality, which in the case of acromegaly or Cushing's disease can be life threatening. Macroadenomas require surgical decompression, most often by transsphenoidal surgery, in order to reduce compression of adjacent structures. For large tumors, surgical removal is the initial treatment of choice. For small prolactinomas, the primary treatment is a dopamine agonist (bromocriptine, or cabergoline). When this is not tolerated or is ineffective, microsurgery is the next step. For acromegaly produced by excessive growth hormone secretion and Cushing's disease caused by excessive adrenal cortisol production, the usual first management option is microsurgery, most often performed via a trans nasal transsphenoidal approach with endoscopic assistance. Hormone improvement is often rapid and effective, and the endocrine result is immediate if the tumor can be removed successfully. In contrast, fractionated radiation therapy is rarely used for such tumors owing to the prolonged latency interval until response, and the radiation fall-off to adjacent critical structures. Nonetheless, between 20 to 30% of patients who undergo surgical removal either do not achieve hormonal remission or suffer tumor recurrence. Approximately 30% of non-functioning tumors recur after initial surgery. Thus, GKRS could be appropriate in roughly 1/3 of cases.

Using GKRS, a tumor margin dose of 12 Gy can stop tumor growth. Higher tumor margin doses (e.g., 18–20 Gy) are required to treat excess hormone secretion. Critical structures adjacent to the tumor target (optic apparatus, brain stem, cavernous sinus) may represent dose limiting structures for the treatment plan. The main risk is hypopituitarism reported in the more serious series to occur in around 20% of the patients in the long term. [61–62] **TABLE 5** presents the number of functional and nonfunctional pituitary adenomas treated with GKRS across different centers. ●

Malignant Tumors

Intracranial Metastases

Gamma Knife Radiosurgery has been used in more than one million patients worldwide and has sparked a revolution in the management of cancer that has spread from a site in the body to the brain. Lung cancer, breast, renal, and melanoma represent the largest number of such cancers. While originally applied to patients only with a single brain metastases as an alternative to craniotomy and removal (followed by whole brain radiation therapy or WBRT), GKRS is now used for patients with one or many brain metastases. The role of WBRT in the management of brain metastases has been a topic of intense debate, with multiple reports presenting data suggesting no survival benefit from prophylactic WBRT, while increasing the risk of leukoencephalopathy and cognitive decline within a year of treatment. [63–65] Increasing evidence indicates that control of brain disease is possible in more than 80% of patients and that death from CNS progression has been reduced to < 20% of patients who undergo GKRS for metastatic brain cancer. The important issue for GKRS is the total volume of all brain metastases to undergo treatment, not the number of such metastases.

The estimated incidence of metastatic brain tumors in USA is 30–50 per 100,000. [13–14] Based on statistics from the American Brain Tumor Association, 20% of patients present with single brain metastases, and more than 80% having multiple metastases. Based on the Leksell Gamma Knife Society report in 2019, close to 41,000 metastatic tumor treatments were reported across the entire world. Increasingly, GKRS has replaced both upfront craniotomy and the reflex initial use of WBRT in patients with newly diagnosed brain metastatic disease. Craniotomy and tumor removal are normally considered in patients with large tumors, usually solitary, associated with symptomatic mass effect, particularly if a diagnosis is yet to be established. WBRT is used upfront in patients with miliary brain metastases or those who present with imaging criteria of carcinomatous meningitis. Increasingly, tumor bed GKRS has replaced WBRT in patients who have undergone craniotomy and tumor removal or debulking. **TABLE 6** presents the number of brain metastatic tumors treated with GKRS between 1968 until 2018 based on the Leksell Gamma Knife Society report.

Glial Tumors

Data from the 2019 Central Brain Tumor Registry of the United States (CBTRUS) estimates that in 2020, the number of new cases of glial brain tumors across the United States will be 23,730 (21,850 malignant, 1,880 non-malignant). Thus, the incidence rate of all primary benign and malignant glial brain tumors is 6.7 cases per 100,000. [11] The most common primary brain tumor remains glioblastoma multiforme, accounting for 48% of malignant brain tumors. [11] CBTRUS previously estimated the 2010 point prevalence rate for all primary malignant brain and CNS tumors to be 47.6 per 100,000, or a total of 103,634 cases. In the 2014 prevalence of selected adult malignant brain tumor histologies, glioblastoma had the highest prevalence, at 9.23 per 100,000 (23,327 cases), followed by diffuse astrocytoma (4.68 per 100,000; 10,868 cases), and oligodendroglioma (3.57 per 100,000; 8,217 cases).

GKRS has proven valuable in the treatment of unresectable, residual, or recurrent juvenile pilocytic astrocytomas, oligodendrogliomas, and anaplastic astrocytomas that have progressed despite initial management with chemoradiation. Recent publications about the role of radiosurgery as a boost for recurrent border zone tumor progression indicate an improved overall and post radiosurgery survival benefit. GKRS has been used in selected glioblastoma (WHO Grade IV) patients after initial diagnosis, cytoreductive surgery when feasible, fractionated radiation therapy (60 Gy over 6–7 weeks), and often adjuvant oral temozolomide. GKRS has been used effectively in residual or recurrent deeply located grade 1 tumors (pilocytic astrocytomas), and as adjuvant for Grade II oligodendrogliomas, fibrillary astrocytomas, and anaplastic astrocytomas (Grade III). **TABLE 7** presents data pertaining to the use of GKRS in the management of low- and high-grade gliomas.

Uveal melanoma

Uveal melanoma is the most common primary malignant tumor of the eye in adults with a total of 2–8 cases/million people per year and a peak in incidence between 55 and 70 years. [15] [66] Several therapeutic approaches and options for this tumor are available: expectant observation with periodic ophtalmological examination only, laser photocoagulation, thermotherapy, resection or enucleation, brachytherapy, charged particle therapy (protons or helium ions) and stereotactic radiotherapy or radiosurgery. When GKRS is applied, adequate fixation is used for eye immobilization during the imaging and the treatment. The most common is retrobulbar local anesthesia and the sutures of two rectus eye muscles. To ensure the build up and homogeneous propagation of radiation between the eye and the air, plastic cover filled with tissue-equivalent gel is used. The treatment results from published retrospective series shows high rate of eye preservation and local control. **TABLE 8** GKRS can be considered as an eye-preserving alternative to enucleation. Its application can be considered even in the location of uveal melanoma at fundus, where brachytherapy is not applicable. ●

MALIGNANT TUMORS CASE MIX 1968–2019

- Malignant Glial Tumor ———— 6%
- Metastatic Tumor ———————— 88%
- Glioblastoma —————————— 1%
- Other Malignant Tumor ——— 5%
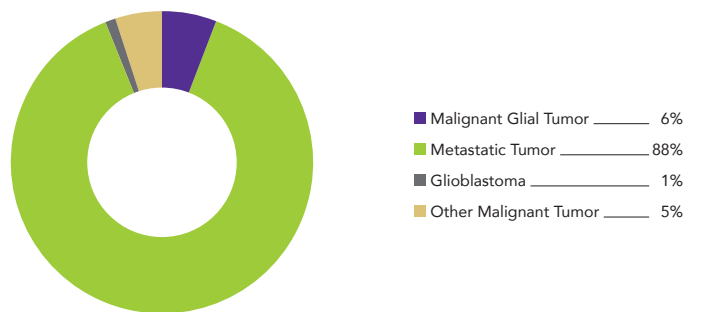
MALIGNANT TUMORS – ACCUMULATED NUMBERS TREATED WORLDWIDE 1968–2019
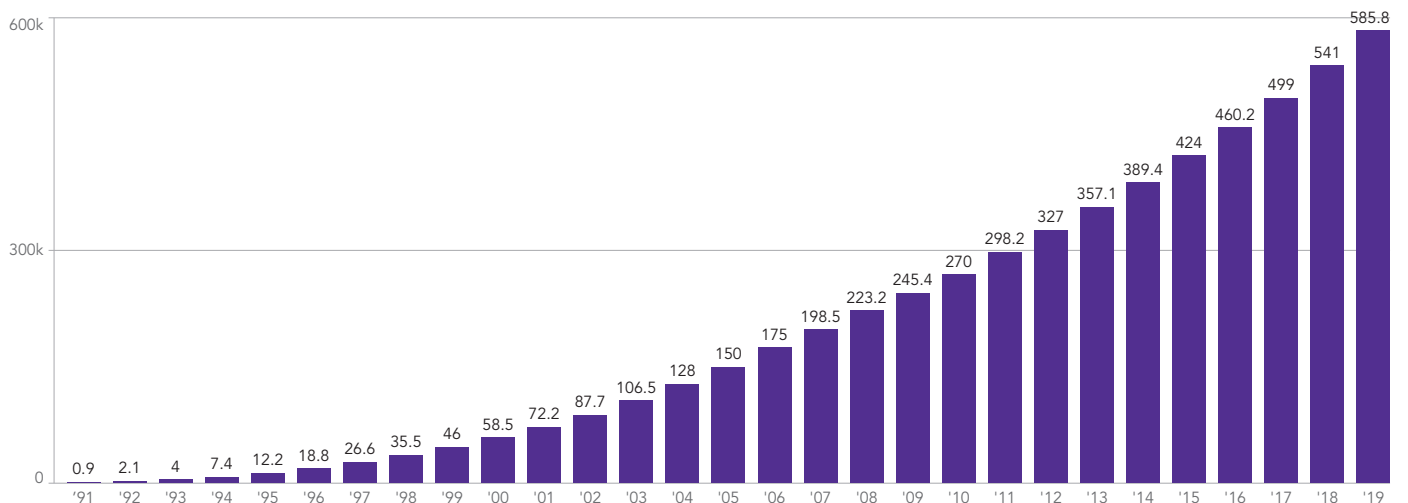
NOTE 1991 reflects cumulative numbers since 1968

Functional Disorders

Movement Disorders

Gamma Knife can be used to perform a VIM thalamotomy primarily for tremor reduction in patients with essential tremor (ET) or tremor predominant Parkinson's disease (PD). Both multicenter and single center experience has been reported using modern localization techniques with MRI when feasible, but also CT imaging when patients are ineligible for MRI. Outcomes suggest that 70–80% of patients will have contralateral tremor suppression with a single 4 mm isocenter delivering a maximum radiation dose of 130–140 Gy directed to the thalamic VIM nucleus. Clinical benefit ensues in 6–12 months. Between 4–6% of patients may have larger than expected lesions detected at follow-up imaging, called "super responders." Some of these patients may have associated neurological symptoms or signs developed related to treatment effects encroaching on the internal capsule laterally or sensory thalamic nucleus (VPL) posterior to the VIM nucleus. Intraoperative physiological confirmation is not performed during GK thalamotomy. In patients with excellent outcomes and no new side effects, a contralateral thalamotomy can be considered no sooner than 12 months after the initial procedure to monitor for improvement of tremor, and identification of adverse radiation events. Based on the 2019 data from Leksell Gamma Knife society report, a total of 372 patients with movement disorders were treated with GKRS. **TABLE 9** presents the number of patients with movement disorders treated with GKRS across different centers.

Parkinson's Tremor

Studies published in the past investigating the age-adjusted incidence of Parkinson's disease in the English and Scottish populations reported annual rates of 12 and 14.6 per 100,000 respectively. The Parkinson's Disease Foundation estimates that by the year 2020, nearly one million people in the US will be living with Parkinson's disease. There are 60,000 new cases identified per year in America (20 per 100,000). Prevalence data was obtained from a recent study (2014) which performed a systematic review and meta-analysis on 219 articles. Forty-seven articles that obtained prevalence data based on a two-stage identifica-

tion procedure which identified individuals with PD in the general population. The prevalence of PD in the general population, stratifying individuals from age 40–80+ was estimated to be 315 per 100,000. [67]

Essential Tremor

Essential tremor (ET) is defined as an isolated bilateral upper extremity action tremor lasting for at least three years. Tremor may also involve other locations, commonly the neck and vocal cords. [68] The worldwide crude prevalence rate of ET in adults ranges from 0.4%–0.6%. [69–70] ET affects approximately 1% of the population and 4–5% of adults over the age of 65. [71] The primary management therapy for ET is medical therapy with beta blockers or primidone. However, in patients with medically-resistant ET, surgical options include deep brain stimulation, high frequency ultrasound, and GKRS. A prospective study with independent blind assessment have nicely demonstrated the very good efficacy and safety of GKRS in tremor. [72]

Epilepsy

Gamma Knife radiosurgery has been used in carefully selected patients with mesial temporal lobe epilepsy as an alternative to amygdalohippocampectomy performed via craniotomy and microsurgical resection. Isolated case reports have described the use of GKRS for other brain epileptic sites confirmed by appropriate neurophysiological studies. GKRS callosotomy has been reported for use in patients with drop attack epilepsy. Most patients undergoing GKRS for epilepsy are treated for seizure disorders in the context of imaging defined lesions such as AVMs, cavernous malformations, and lower grade glial neoplasms. In the field of epilepsy surgery, SRS demonstrates safety efficacy in the treatment of hypothalamic hamartomas (HH). [73] Epileptic HH are frequently associated with severe cognitive and psychiatric comorbidities. SRS is the reference technique for small HH. Prevalence of HH is estimated to be 1 in 50 000 to 100 000. The selection of options to manage patients with epilepsy requires multidisciplinary input.

FUNCTIONAL DISORDERS – ACCUMULATED NUMBERS TREATED WORLDWIDE 1968–2019
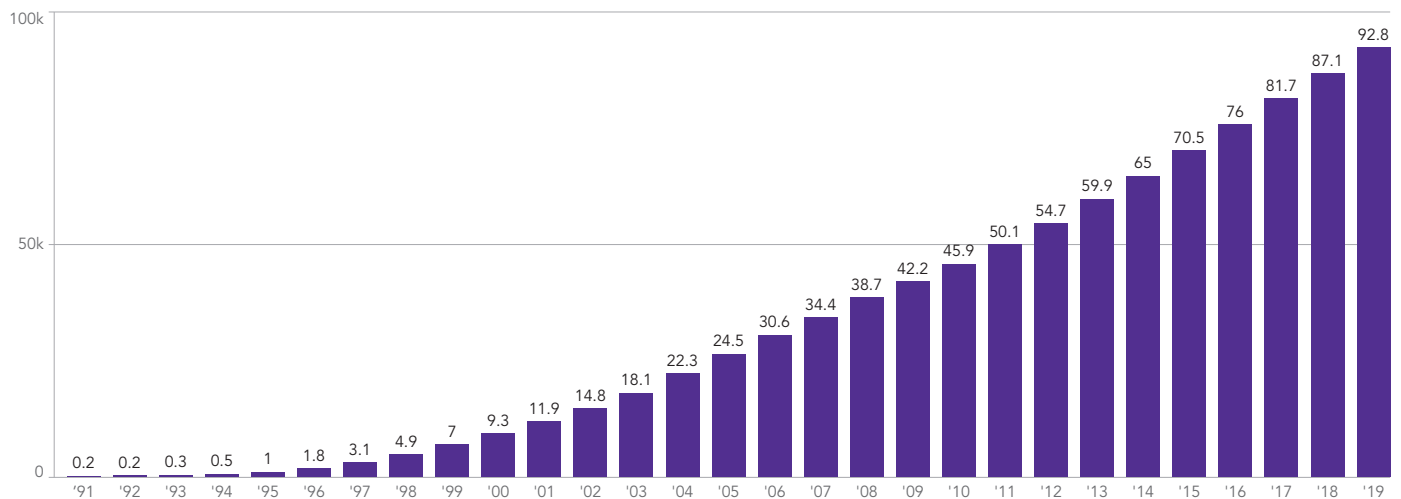
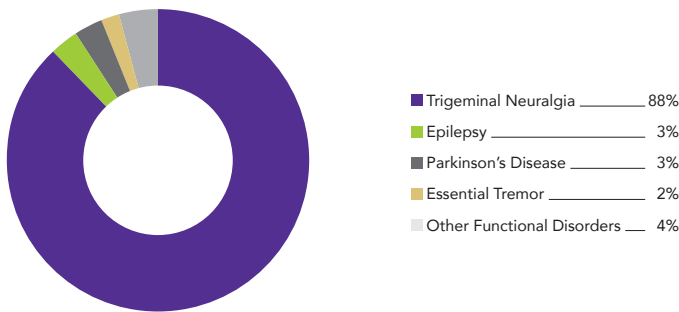NOTE 1991 reflects cumulative numbers since 1968

There are several studies that review the epidemiology of epilepsy as stratified by socioeconomic status, age, race and geographic location. To gain a comprehensive understanding for the incidence and prevalence in the general population, a meta-analysis and systematic review of the epidemiology of epilepsy was reviewed. In the review, 33 studies were used to determine these statistics based on the level of development of the country (high income vs. low income). The mean incidence of epilepsy for both high and low income countries was 50.4 per 100,000 (High income = 45; Low income = 81.7). [74] Other studies have noted an annual incidence rate between 15 and 71 per 100,000 in the United States. Another epidemiological study published in 2013 by Kaiboriboon, et al. estimated the prevalence of epilepsy to be 5–9 per 1,000 in the United States. [75] Overall, and based on the Leksell Gamma Knife Society report, between 1968 and 2019, a total of 2,855 patients underwent GKRS for epilepsy management.

Behavioral Disorders

The purpose of GKRS in treating psychiatric disorders is to improve a series of specific symptoms caused by mental illnesses. The aim of radiosurgery is to block certain limbic system pathways associated with specific psychiatric disorders. This may enhance brain function, with patients experiencing relief from certain symptoms. GKRS is often reserved to patients with symptoms resistant to conventional medical and psychiatric therapy. GKRS is used in the context of obsessive-compulsive disorders (OCD), major depression (MDD) and anorexia nervosa.

Based on statistics from the National Alliance of Mental Health, 19.1% of US adults experienced mental illness in 2018, representing one of five adults. The prevalence of OCD was estimated to be 1.2% (3 million people), the prevalence of MDD was 7.2% (17.7 million people), and the prevalence of anorexia nervosa has been reported to

FUNCTIONAL DISORDERS CASE MIX 1968–2019

- ■ Trigeminal Neuralgia —————— 88%
- ■ Epilepsy ————————————— 3%
- ■ Parkinson's Disease ————— 3%
- ■ Essential Tremor —————— 2%
- ■ Other Functional Disorders — 4%

be between 0.3–0.9%. [76] Among these psychiatric disease a demonstration of the safety efficacy of radiosurgery exist only for OCD. [77–78] SRS for depression and anorexia nervosa are more debatable indications still investigational.

Trigeminal Neuralgia

The initial treatment of trigeminal neuralgia (TN) is medical with agents such as carbamazepine, oxcarbazepine or gabapentin. These medications do not work in all patients or if they work initially, the effect can diminish over time. For medically refractory patients or those intolerant of side effects of such medicine, microvascular decompression (MVD) remains the current "gold standard" surgical intervention for patients who are eligible for craniotomy. Percutaneous treatments using glycerol rhizotomy, radiofrequency, or balloon-assisted rhizotomy are alternative strategies as well. GKRS has been shown to be a reliable and safe alternative in many published reports. Outcomes are best when patients have not already failed prior surgical procedures. Pain relief after GKRS typically occurs two to four weeks after the procedure. A study from Italy suggested that the prevalence of TN was 100–200 per million. The incidence is 50–200 per million in patients over age 60. **TABLE 10** presents the number of patients with TN treated with GKRS across different centers.

The annual incidence in the United States is 5.9 per 100,000 women, and 3.4 per 100,000 men. European population-based studies in the UK and the Netherlands suggest that the annual detection rate is significantly higher and ranges between 126–289 cases per million. [6–7] In a prospective UK study, a General Practice Linkage Scheme with the National Hospital for Neurology and Neurosurgery (NHNN) was used to ascertain all cases of neurological disorders over an 18-month period in an unselected urban population of 100,230 patients registered, based on 13 general practices in the London area. In three of these practices (27,657 persons), lifetime prevalence was also assessed. Registration of patients began in 1994; this report covers the period from January 1, 1995 to July 1, 1996. This survey does not include the small number of patients who are in long-stay hospitals for severe neurological problems. The age, and sex-adjusted incidence rate of TN was reported as 8 per 100,000. The lifetime prevalence was reported as 0.7 per 1,000 population. This is the first large, prospective UK study measuring the burden of all serious neurological conditions in the community in over 30 years. A German, population-based study conducted in 2011 estimated the lifetime prevalence of TN to be 0.3% (10 of 3,336; 95% CI [0.1%–0.5%]). [79] Another study focusing on the Egyptian population estimated an age-specific, lifetime prevalence rate among subjects over 30 years of age was 29.5 per 100,000 (95% CI 22.3–34.7) (n = 4/13,285 persons). [80] ●

Tables

TABLE 1 ARTERIOVENOUS MALFORMATIONS

Location	Treatment period	Number of patients	Number per year
Prague–Czech Republic, Liscak et al. 2007	1992–2000	330	41.25
Pittsburgh–USA, Kano et al. 2012	1987–2012	1130	45.2
Tokyo–Japan, Hasegawa et al. 2018	1990–2013	732	31.8
Cairo–Egypt, El Shehaby et al. 2019	2009–2015	29	4.8
Virginia–USA, Hung et al. 2019	1989–2012	1159	50.4
Busan–Republic of Korea, Kim et al. 2019	2002–2017	608	40.5

TABLE 2 CAVERNOUS MALFORMATIONS

Location	Treatment period	Number of patients	Number per year
Chengdu–China, Liu et al. 2016	2009–2014	43	8.6
Seoul–Republic of Korea, Sheen et al. 2018	2003–2008	95	19.0
Seoul–Republic of Korea, Park et al. 2018	1998–2011	87	3.8
Pittsburgh–USA, Jacobs et al. 2019	1988–2016	148	5.2

TABLE 3 VESTIBULAR SCHWANNOMAS (ACOUSTIC NEUROMAS)

Location	Treatment period	Number of patients	Number per year
Brussels–Belgium, Delbrouck et al. 2011	2000–2011	415	37.7
Rotterdam–Netherlands, Kano et al. 2016	2002–2010	604	75.5
Seoul–Republic of Korea, Kim et al. 2017	2007–2014	265	37.8
Vienna–Austria, Frischer et al. 2018	1992–2016	618	25.75
Tokyo–Japan, Hasegawa et al. 2018	1991–2013	872	36.3
Seoul–Republic of Korea, Lim et al. 2019	1999–2018	389	20.5
Stanford–USA, Santa Maria et al. 2019	1992–2013	579	27.5
Pittsburgh–USA, Johnson et al. 2019	1987–2019	1954	61.1

TABLE 4 MENINGIOMAS

Location	Treatment period	Number of patients	Number per year
Seoul–Republic of Korea, Jang et al. 2015	2008–2012	628	157.0
Seoul–Republic of Korea, Seo et al. 2018	1998–2010	770	64.4
Virginia–USA, Gupta et al. 2019	1994–2015	1375	65.5
Pittsburgh–USA, Faramand et al. 2019	1987–2018	2022	65.2
Taiwan–China, Hung et al. 2019	1993–2011	790	43.9

TABLE 5 PITUITARY ADENOMA

Location	Hormone	Treatment period	Number of patients	Number per year
Multicenter report, Hung et al. 2019	Prolactin	1997–2016	289	15.2
Multicenter report, Ding et al. 2019	Growth Hormone	1990–2016	371	14.2
Multicenter report, Mehta et al. 2017	ACTH	1990–2016	278	10.7
Multicenter report, Lee et al. 2014	Nonfunctional	1998–2012	569	40.6

TABLE 6 METASTATIC TUMORS TREATED WITH GKRS FROM 1968–2019 BASED ON THE LEKSELL GAMMA KNIFE SOCIETY REPORT

Location	Number of patients
Asia	270,512
Europe	89,077
Latin America	1,779
Middle East and Africa	1,936
North America	149,846

TABLE 7 GLIOMAS

Location	Treatment period	Number of patients	Number per year
Cleveland–USA, Einstein et al. 2012	2002–2007	35 (GBM)	7.0
Seoul–Republic of Korea, Kong et al. 2008	2000–2006	49 (Grade III), 65 (GBM)	18.2
Pittsburgh–USA, Niranjan et al. 2015	1987–2008	297 (GBM)	14.1
Prague–Czech Republic, Guseynova et al. 2018	1992–2014	126 (GBM)	5.7
Multicenter report, Kano et al. 2019	1988–2016	89 (ependymoma)	3.2
Cleveland–USA, Murphy et al. 2019	1990–2016	141 (pilocytic astrocytoma)	5.4

TABLE 8 UVEAL MELANOMA

Location	Treatment period	Number of patients	Number per year
Prague–Czech Republic, Simonova et al. 2002	1996–2001	81	16.2
Milan–Italy, Modorati et al. 2020	1993–2018	194	7.8
Boston–USA, Joye et al.	2000–2012	23	1.9
Indianopolis–USA, Fakiris et al. 2007	1998–2004	19	3.2
Busan–Republic of Korea, Kang et al. 2012	1998–2006	22	2.8

TABLE 9 MOVEMENT DISORDERS

Location	Treatment period	Number of patients	Number per year
Seattle–USA, Young et al. 2010	1994–2007	172 (ET)	13.2
Lubbock–USA, Mark et al. 2011	1991–2010	120 (PD) 76 (ET)	10.3
Pittsburgh–USA, Niranjan et al. 2017	1996–2015	91 (ET)*	4.7
Pittsburgh–USA, Raju et al. 2018	1998–2012	15 (MS)**	1.0

*Essential Tremor **Multiple Sclerosis

TABLE 10 TRIGEMINAL NEURALGIA

Location	Treatment period	Number of patients	Number per year
Pittsburgh–USA, Kondziolka et al. 2010	1992–2007	503	33.5
Winston Salem–USA, Lucas et al. 2014	1999–2008	777	86.3
Marseille–France, Regis et al. 2016	1992–2010	737	40.9
Taiwan–China, Lee et al. 2018	2006–2014	108	13.6
St. Petersburg–Russia, Bervitskiy et al. 2019	2009–2016	52	7.4
Multicenter report, Xu et al. 2019	1994–2015	263 (MS–TN)*	12.1

*Multiple Sclerosis related TN

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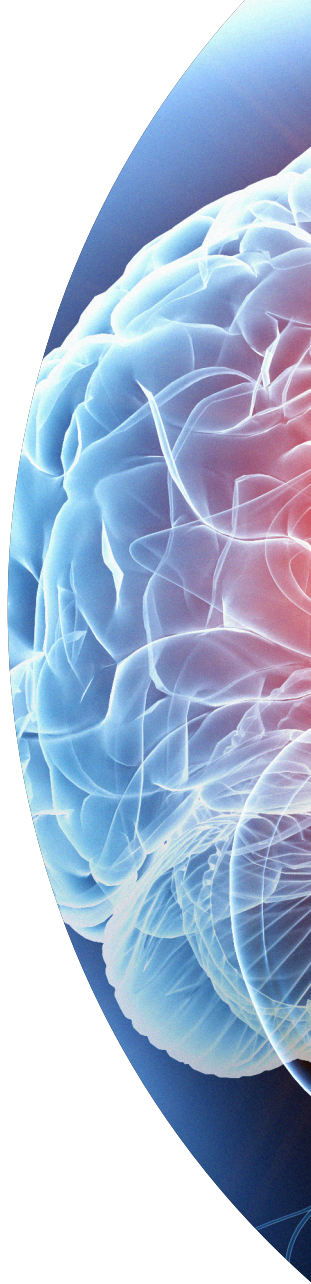
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