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First Thousand Cases of Intracranial Radiosurgery Treated with Gamma Knife at a Tertiary Care Hospital in India

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Abstract

Purpose We present the profile of first 1,000 cases of intracranial radiosurgery (IRS) treated with Gamma Knife system at a government-funded tertiary care hospital in India. In addition to the information on the indications treated, this study provides an idea of the relevance of the Gamma Knife Radiosurgery (GKRS) for IRS in the fast-changing technological scenario. This study also shows the disease indications for which GKRS was the primary treatment preference.

Materials and Methods Leksell Gamma Knife model 4C was used for GKRS. Leksell G-frame-based stereotactic localization was used for all patients. Axial magnetic resonance imaging scans were used for treatment planning with additional two-dimensional angiography images for patients treated for arteriovenus malformations (AVM). The patient population treated with GKRS at our center mainly comprised of patients referred from across the country.

Results Acoustic schwannoma formed the largest group of patients (27%) followed by meningioma (21%), AVM (18%), pituitary adenoma (16%), brain metastasis (5.3%), trigeminal neuralgia (3%), cavernoma (2.4%), glomus jugulare (1.8%), craniopharyngioma (1.1%) and “others” (5%).

Conclusion The case mix at our center is similar to the overall Indian case mix. However, it is different from the Asian data of 2018 but interestingly similar to the data from Middle East and Africa for 2018. Among the various categories of cranial disorders treated by us, pituitary adenoma tumors had minimum (14/161) and cavernoma tumors had maximum (24/24) proportion of cases managed with GKRS as primary treatment modality.

Keywords
- case mix
- Gamma Knife
- intracranial disorders
- stereotactic radiosurgery

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Introduction

Stereotactic radiosurgery (SRS) is a term used to describe stereotactically-guided high-precision conformal irradiation of a target volume in a single session as against the multisession (fractions) dose delivery in conventional radiotherapy. The main attributes of a SRS technique are high geometric accuracy, high conformality, and sharp dose fall-off beyond the target volume. The disorders that are suitable for SRS should be small and have well-defined margins on three-dimensional imaging modalities such as computed tomography and magnetic resonance imaging (MRI). Many types of intracranial lesions, benign as well as malignant ones, meet the criteria of suitability for SRS.

There are many technologies available for delivering SRS, but the longest experience has been with the Gamma Knife system. The first clinical prototype Gamma Knife system for research developed by the famous Swedish neurosurgeon Lars Leksell along with his physics colleague B Larsson was ready in the year 1967.[1] Over 300 Leksell Gamma Knife (LGK) units have been installed worldwide in the past 15 years (till 2018) for treating various types of intracranial conditions. More than 88,000 indications were treated in 2018 and over 1.2 million patients have been treated through 2018 by Gamma Knife alone.[2]

The Gamma Knife-based SRS (GKRS) technology has evolved considerably since its inception in 1968. Its collimator design, patient positioning system, and the computer-based treatment planning system have all undergone significant changes leading to improved treatment delivery accuracy, dose conformality, shorter treatment time, and ease of operations. It is interesting to note that even with the emergence of many linear accelerator-based robotic SRS technologies, GKRS system is still considered as a "gold standard" for cranial SRS in terms of accuracy and simplicity of operations. The accuracy achievable in physical dose delivery is within 0.5 mm with GKRS.[3]

There have been studies from many Gamma Knife centers around the world revealing the variations in application of GKRS in treating various intracranial disorders.[2,4–6] The variations became larger if one compared centers from different countries or continents. The factors that most likely influence the composition of indications treated with GKRS at a center are (i) expertise available in the hospital not only in the neurosurgery domain but also in the other closely connected fields such as interventional radiology, oncology and medical physics; (ii) disease profile of the population being served by the hospital; (iii) reputation of the center for GKRS expertise; and (iv) perceived relevance of Gamma Knife system for SRS among the referring physicians as well as the patient population.

Ours is a government-funded tertiary care hospital with a team of well-trained experts at the GKRS center. The hospital also has well-developed specialties in the closely connected disciplines, and a structured referral system from hospitals spread across the country. We performed a retrospective analysis of the first 1,000 cases treated at our center in terms of diagnosis, tumor size, and other related details. We believe that this study would provide a reasonably good idea of the relevance of the GKRS system for cranial SRS in the fast-changing technological scenario in India. This study would also show if GKRS was the first choice or a last resort kind of option for the patients. However, our study is neither about the incidence rate of various intracranial disorders nor about determination of appropriateness of GKRS for these disorders in India.

Materials and Methods

Gamma Knife System and Procedure

The LGK model 4C (Elekta, Sweden) used in this study had a distinctive addition over the earlier LGK models namely the automatic positioning system (APS). The APS obviated the need of manual co-ordinate setting (trunnion system) for each isocenter (shot) to execute a treatment delivery. The APS moved the patient head from one shot to another within one helmet size (run) without the need for the operator to enter the treatment room for manual change of shot coordinates, as was the practice with the earlier trunnion-based systems. The main advantages of the APS included speeding up of the treatment delivery, less chances of human error in setting up the coordinates manually, and a possible reduction in manpower requirement. However, another less appreciated advantage was the fact that a treatment planner could afford to use a larger number of shots to improve conformality of a treatment plan, if needed. The LGK 4C had four collimator helmet sizes of 4, 8, 14, and 18 mm like the earlier LGK models. A brief description of the evolution of LGK machines since 1967 is provided at the end of this section for the ready refence of the readers.

After fixation of the stereotactic frame (Leksell G-frame) on the patient head, which was MRI compatible, all patients underwent MRI scans either on a 1.0 Tesla Magnetom Harmony or 1.5 Tesla Magnetom Avanto (Siemens Healthcare, Erlangen, Germany) with the MR localizer. The patients being treated for arteriovenous malformations (AVM) underwent additional imaging in the form of a planar digital subtraction angiography on Axiom Artis BA machine (Siemens, Germany) with the G-frame and special angiography localizer.

The images were then exported to the Leksell Gamma Plan (LGP) for treatment planning. The LGP version 5.34 and later 10.0 (Elekta, Sweden) were used for treatment planning. While preparing a plan, dose conformity and radiation tolerance of adjacent organs at risk (OAR) or normal brain tissue were our primary optimization objectives.

The first clinical LGK machine for research developed by the famous Swedish neurosurgeon Lars Leksell along with his physics colleague B Larsson was ready in the year 1967. Following its success, commercial models starting from LGK model U (1987), Model B(1988), Model C/4C(1999), Model Perfexion (2006), and Model Icon (2016) were launched. Each came with improved accuracy and efficiency in treatment delivery. Till LGK 4C, 201 Co-60 sources were distributed in a hemispherical geometry in five rings. The first major change in terms of automation in treatment delivery was a feature called APS provided with LGK 4C which obviated the need of manual trunnion-based coordinate setting. The significant next step was a complete redesigning of the collimator system for Perfexion. The four external helmets/collimators (4mm, 8mm, 14mm, and 18mm) were replaced with automatically changing three internal collimators (4mm, 8 mm, and 16 mm). The number of sources was now 192 distributed on a conical surface in five rings. In addition, the introduction of a highly accurate couch-based patient positioning system (PPS) made the limited movement APS redundant. Further, there was more space within the internal collimator system and hence accessibility of peripheral tumors improved considerably. Overall, Perfexion improved the treatment delivery efficiency with the introduction of automatic treatment delivery without compromising the accuracy. Icon system added on-board cone-beam computed tomography to the Perfexion. This has opened new avenues for mask based fractionated SRS.

Patients

The patient population treated with GKRS at our center mainly comprised of patients referred from across the country. From the referring hospitals, generally, either the neurosurgeons or a team comprising of radiation oncologists and head-and-neck surgeons referred the patients to our center for GKRS. The patients were then reassessed at our center by the GKRS specialist team as per our institutional policy. The policy adopted by us was in line with international practice—patients with benign lesions/metastases having volumes less than approximately 13 cc were considered suitable for GKRS. Such cases when found inoperable or on patients' preference were taken up for GKRS. Occasionally, a primary cranial malignancy was also chosen for GKRS. In some cases, larger volumes were also considered for want of any other safer treatment modality. Large AVMs fell in this category. Volume-staged GKRS with a gap of 4 to 6 months between the two GKRS sessions was performed in such cases. An interventional radiologist was mandatorily part of the GKRS team in the case of AVM. Most of the cases treated with volume-staged GKRS were treated in two stages,[7] and a few rare ones in three stages. The part of the volume containing either the main nidus or the part that was close to any critical structure was considered for the first session of GKRS. The volume division was based on certain anatomical landmarks to ensure easy identification for dose matching later with the remaining part of the volume to be considered for second session of GKRS. The second session of GKRS was delivered after 4 to 6 months of the first session. The dose in the second session was usually approximately 2 Gy less than the first GKRS session. Deliberate efforts were made to avoid or minimize dose spills between the two parts of the AVM volume. In large AVMs where volume-staged GKS was either ruled out due to patient's preference or was considered risky due to potentially high-dose region overlap between the volumes, an unconventionally low dose covering the entire AVM volume was delivered as a last option of treatment. The patient was kept on follow-up to assess for reduction in nidus volume. If the nidus volume shrank noticeably between 6 and 12 months or even later post-GKRS, then another GKRS session with still lower dose was planned.

Occasionally, a medical physicist connected with the GKRS facility was also consulted on technical feasibility in situations such as extremely peripheral location of the tumor or presence of a critical OAR in close vicinity of the tumor. During case selection for GKRS, we realized early on that there was a learning curve for the entire team. The first most important learning was that due to space constraints within the helmet system of LGK 4C, frame fixation was critical for feasibility of treatment execution for tumors/targets that were located at extreme periphery of the skull. It warranted positioning of the frame in such a way to keep the tumor well inside the four sides and well above (at least ~20 mm) the top edge of the G-frame. To facilitate the fixation of the frame at the appropriate position, we decided to keep MRI scans of the patient on display in all three major planes in the cubicle where the frame was being fixed by the neurosurgeon. We also realized that the frame once fixed needed to be tested to ensure that the pins holding frame to the scalp were tight enough to prevent their movement/slippage afterwards. Any movement/slippage of the pins from their position after the imaging meant repetition of the entire process all over again either on the same day or on the next available GKRS slot. In the case of multiple tumors, the team identified, in advance, the tumors that could be irradiated in one session and accordingly positioned the frame fixation on the skull to avoid potential collisions with the helmets during treatment execution.

All patients, right from the first case till the 1000th case, were included in the study. Diagnosis for benign tumors was clinical and image based if prior surgery or biopsy was not performed.

Results and Discussion

The various types of intra cranial disorders treated with GKRS at our center are summarized in ►**Table 1**. It is observed that acoustic schwannoma (AS) formed the largest group of patients (27%) followed by meningioma (21%), AVM (18%), pituitary adenoma (PA; 16%), metastasis (5.3%), trigeminal neuralgia (3%), cavernoma (2.4%), glomus jugulare (1.8%), craniopharyngioma (1.1%), and "Others"(5%). The "Others" category clubbed all the less frequent cases treated at our center for broad categorization purposes. It included all cases of malignant tumors, except metastases, and other less frequent benign conditions. Of the 50 disorders in this category, 39 were benign tumors such as paraganglioma, schwannomas other than AS, and neurofibromatosis type 2. The malignancies in this category were mainly recurrent type that included low- and high-grade astrocytomas, hemangiopericytoma, medulloblastoma, adenocystic carcinoma orbit, pineal papillary carcinoma, and carcinoma maxilla.

For ease of analysis and comparison with other centers, we divided the 1,000 cases in four broad categories namely benign tumors, vascular disorders, malignant tumors (including metastases), and functional disorders. The proportion of cases in these categories was 70.8, 20.1, 6.4, and 2.7% in that order. Thus, the benign disorders formed the largest proportion of all the indications treated at our center.

Table 1 Summary break-up of 1,000 cases treated with Gamma Knife at our center

Sr no.	Diagnosis	Total no. of cases	Male	Female	Age in years Median (range)	Lesion volume (cc) Median (range)	Primary[a]	Dose (Gy) Median (range)
1	Acoustic schwannoma	271	148	123	48(12–75)	2.33(0.07–36.2)	181	12(11–13)
2	Meningioma	208	75	133	52(11–88)	4.22(0.29–17.1)	114	13.9(10–16)
3	Arteriovenous malformation	177	118	59	30(6–75)	3.6(0.05–18.8)	151	20 (12–25)
4	Pituitary Adenoma	161	89	72	41.5(13–81)	3.7(0.09–16.1)	14	19(11–25)
5	Metastasis	53	25	28	53(33–74)	0.77(0.11–4.8)	52	18(15–23)
6	Trigeminal neuralgia	27	17	10	58.5(44–80)	NA	26	80 (70–80)
7	Cavernoma	24	15	9	34(3–57)	1.5(0.2–8.4)	24	16(11.5–22)
8	Glomus Jugulare	18	5	13	41(29–76)	3.55(1,1–11)	7	18(13–20)
9	Craniopharyng-ioma	11	10	1	28(14–50)	4.6(0.8–5.3)	2	12(10–14)
10	Others	50	28	23	NR	NR	NR	NR

Abbreviations: NA, not applicable; NR, not relevant.
[a]Primary: Gamma Knife radiosurgery as primary treatment.

The overall Indian data between 1997 and 2018 shows the proportion of these categories at 67.3, 21.6, 6.5, and 4.6% in that order, which is close to our data.[2] The Indian case mix for the year 2018 is close to the overall case mix between 1997 and 2018. Our present data shows similar pattern. The situation is somewhat similar to the one prevailing in North America during early 1990s when the vascular and benign tumors formed the largest proportion of all the cases treated with GKRS. But the present trend in North America is very different. In 2018, 63% of the cases treated with GKRS were in the malignant category followed by benign tumors (23.2%), functional disorders (10.1%), and a minor proportion of vascular/ocular disorders.[2] The GKRS case mix of Asia for 2018 is also different from our data. The malignant tumors formed the largest group (48.5%) followed by benign tumors (38%) and vascular disorders (9.5%) in Asia. Japan has a very unique statistic for GKRS. In the year 2018 the case mix revealed predominantly malignant tumors (74.1%) being treated with GKRS followed by benign tumors (19.5%) in Japan. Interestingly, the data from Middle East and Africa for 2018 is similar to our data with benign tumors (67.7%) followed by vascular disorders (13.2%), malignant tumors (12.5%) and functional disorders, and others (6.6%).[2]

As shown in ►**Table 1**, 181 out of 270 patients, that is,67% of AS cases, GKRS was the primary treatment. These patients either had small tumor volumes or were considered as risk for open surgery due to their associated medical condition/age or they opted for GKRS in place of surgery. Hearing status was assessed by pure tone audiometry before the GKRS. Sixty-eight of two-hundred seventy-one patients had either complete hearing loss or no functional hearing in the affected side before GKRS. The institutional protocol for dose prescription was 12 Gy at the tumor margin. However, proximity of critical structures such as brain stem and cochlea around the tumor sometime did not allow the 12 Gy prescriptions. At times tumor coverage was compromised to spare the OARs. Patient's informed consent was taken on such occasions.

Among the top four disorders treated at our center with GKRS, PA tumors were the ones with minimum percentage (9.9%) for which GKRS was a primary treatment. Probably, less invasiveness of the transnasal trans-sphenoidal procedure for PA was the reason for this. In the case of functional PA, which constituted 46% (67/145) of all PAs, quicker symptom relief expected from surgery could be another reason for choosing it over GKRS. Also, 51/145 PA cases had diminished vision. Most of these patients were nonfunctional PAs who needed faster interventions to stop further deterioration of vision/improvement in vision. In the case of cavernoma, GKRS was the primary treatment for all the cases. About 50% of all the cavernoma cases were pontine cavernoma. In the case of AVMs, 18/177 cases were treated in two stages and one in three stages due to large volumes of the nidus. Of the 53 cases of metastasis treated, 28 cases of single metastasis, 23 cases of two metastatic tumors, and 02 cases of three tumors were treated in single sessions.

As for reirradiation, four cases of PA, three cases each of AS and AVM, and one case each of meningioma and trigeminal neuralgia (TN) were reirradiated. The GKRS reirradiation interval average was 3 years. In the case of PA, the reirradiation was after external beam radiation therapy for all the four cases.

A retrospective review of first 1,017 radiosurgery treatments for intracranial lesions by Bir et al[5] at Louisiana

State University Health- Shreveport, Los Angeles, United States, between 2000 and 2013 revealed the following statistics: AS(82), meningioma (136), metastatic brain tumors (298), astrocytoma (49), PA (92), AVMs (85), and TNs (169). The University of Pittsburgh, United States treated a total of 13,500 cases with GKRS from 1987 to 2015. The composition of the cases was 44% malignant tumors, 34% benign, 13% vascular, and 9% functional.[8] Our data differs from this statistic. One major difference is in the proportion of metastatic brain tumors. At our center, it is the fifth largest number (53) as compared with being the largest in the two quoted studies. The worldwide statistics (2018) is also in line with the quoted studies for metastatic tumors. Similarly, share of benign tumors is over 60% in our case as compared with 36.9% of the worldwide data of 2017. As for functional disorders, in our case the share is 2.7% as against 16.9% of Bir et al.[5] The worldwide share of functional disorders in 2018 was 6.1%. The reasons for these variations could be many. As mentioned in the introduction section of this article, incidence rate, preferences of the treating experts as well as that of patients, reputation of a center, and even local sociocultural factors could be responsible for the variations. Hamilton et al[4] in their worldwide survey on potential utilization of GKRS showed that the role of GKRS for meningiomas, metastatic tumors, and AVMs had the highest consensus among centers worldwide. In contrast there were considerable differences among centers with regard to the management of pituitary tumors and craniopharyngiomas. In North America, among the 33,718 cases of benign conditions treated in 2018, the most common ones were meningiomas (42.4%), followed by AS (24.6%), and PA (14%).[2] At our center, 42% of the benign tumors were AS, 32.6% were meningioma, and 25.2% were PA. In a study by Boari et al,[7] 72.5% of the AS tumors underwent GKRS as primary treatment that is comparable to our practice of 69.5%.

A perspective on the usage of GKRS and differences and similarities of our data with the overall worldwide data can be formed from the latest report (2019) of the Leksell Gamma Knife Society.[2] The report showed that more than 1.2 million patients had been treated with GKRS from 1968 till 2018. As per the report, of the approximately 7,000 total indications treated worldwide in the year 1991, the share of malignant tumors was far less than benign tumors and vascular disorders. The situation in 2018 became quite different though. Of the total of over 84,000 indications treated in 2018 the share of malignant tumors went up substantially (47.4%) as compared with benign tumors (37.9%). At the same time, the share of vascular disorders decreased from over 50% in 1991 to approximately 8.3% in 2018. Another trend visible worldwide was the increasing share of functional disorders being treated with GKRS from about nil till 1993 to 6.1% in 2018.

Conclusion

We have presented the profile of first 1,000 cases treated at our center with GKRS. The case mix at our center is similar to the overall Indian case mix. However, it is quite different from the international data of most of the regions/countries except for the Middle East and Africa. Any country or region has its own established practice borne out of years of experience and hence the treating and referring doctors, and also the clientele develop bias for certain treatment modality. The bias may have scientific logic but the best technological solution may not always be chosen due to this bias. For example, Japan has the highest density of GKRS units per capita in the world. Also, their case mix is quite unique with an overwhelming proportion of cases treated with GKRS being malignant tumors. Among the various categories of cranial disorders treated by us, PA tumors had minimum (8.6%) and cavernoma tumors had maximum (100%) proportion of cases managed with GKRS as primary treatment modality. Availability of GKRS has indeed helped the neurosurgeons optimize surgery to mitigate the risks of surgical morbidity. For example, in the cases of AS, meningiomas, or PAs, if complete resection is fraught with potential morbidity, then a part of the tumor can be left behind to be later tackled with GKRS. With more awareness about GKRS in the peripheral referring hospitals and emphasis on quality of life, we too expect more cases of brain metastases being treated with GKRS in place of whole brain radiotherapy. A well-trained and motivated team comprising of neurosurgeons, radiation oncologists, and medical physicists is a must for safe and effective GKRS. In addition, interventional radiologists for AVM and other vascular lesions and head and neck surgeons for AS also need to be involved for optimum case selection. Close and cordial coordination with radiological imaging center of the hospital, especially with the MRI facility, helps a great deal in creating smooth workflow and optimal imaging sequences. The clinical outcome study based on long-term follow-up for the first 1,000 cases is currently being analyzed systematically. However, a preliminary assessment of the data indicated that our results are broadly in line with the published studies world over. For example, at a minimum of 2 years follow-up, the tumor control rates for AS and meningioma are over 90% with less than 5% major adverse radiation reactions such as tumor swelling or edema requiring surgical intervention.[9]

Conflict of Interest
None declared.

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