

The evolution of a clinical registry during 25 years of experience with Gamma Knife radiosurgery in Pittsburgh

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Object. The first North American 201 cobalt-60 source Gamma Knife surgery (GKS) device was introduced at the University of Pittsburgh Medical Center in 1987. The introduction of this innovative and largely untested surgical procedure prompted the desire to study patient outcomes and evaluate the effectiveness of this technique. The parallel advances in computer software and database technology led to the development of a registry to track patient outcomes at this center. The purpose of this study was to describe the registry's evolution and to evaluate its usefulness.

Methods. A team was created to develop a software database and tracking system to organize and retain information on the usage of GKS. All patients undergoing GKS were systematically entered into this database by a clinician familiar with the technology and the clinical indications. Information included patient demographics and diagnosis as well as the anatomical site of the target and details of the procedure.

Results. There are currently 11,738 patients in the database, which began to be used in August 1987. The University of Pittsburgh Medical Center has pioneered the evaluation and publication of the GKS technique and outcomes. Data derived from this computer database have facilitated the publication of more than 400 peer-reviewed manuscripts, more than 200 book chapters, 8 books, and more than 300 published abstracts and scientific presentations. The use of GKS has become a well-established surgical technique that has been performed more than 700,000 times around the world.

Conclusions. The development of a patient registry to track and analyze the use of GKS has given investigators the ability to study patient procedures and outcomes. The future of clinical medical research will rely on the ability of clinical centers to store and to share information.

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THE field of stereotactic radiosurgery was defined by Lars Leksell in 1951.⁴ Interestingly, his first report was initially rejected by the journal to which he submitted the article; the editors informed Leksell that there is no such thing as radiosurgery. In 1967 the prototype Leksell Gamma Knife became the first dedicated radiosurgical technology put to practical use in a hospital environment. Clinical use was restricted to only 4 centers by 1987 and fewer than 1000 patients had undergone radiosurgery for a variety of disorders that included pain, movement disorders, refractory anxiety disorders, brain tumors, and vascular malformations. As a result, the peer-reviewed literature was sparse and consisted primarily of small case series and individual case reports.

Abbreviations used in this paper: GKS = Gamma Knife surgery; HIPAA = Health Insurance Portability and Accountability Act; UPMC = University of Pittsburgh Medical Center.

In 1987, the first 201-source Leksell Gamma Knife entered clinical operation at the UPMC. The field was considered innovative, potentially disruptive to current practice, controversial, and lacking in outcomes data. Installation of the Gamma Knife unit in Pittsburgh proved to be an arduous task, and required more than 4 years of preparatory work to secure local approval and funding as well as regulatory approval from the FDA and the Nuclear Regulatory Commission.⁵ A method to record and store observations made in the initial patients as well as to track long-term clinical outcomes was critical. To facilitate this task we created a clinical registry to manage patient record keeping on a prospective basis. Our hypothesis was that such a registry would help us and other, future sites to understand the potential benefits as well as the risks of this potentially game-changing technology.

Twenty-five years ago physicians kept track of interesting patients by using note cards and charts filed

in various locations—for example, offices, hospital record rooms, and imaging sites. Only in recent years have electronic medical records replaced these unreliable and cumbersome methods. Patient charts were commonly kept in separate areas of the hospital that were not easily accessible to physicians. Prior to the first GKS patient procedure on August 14, 1987, the neurosurgical team at our center realized that a new longitudinal system of data collection was necessary to enter and track patient outcomes. We created a new computer database designed to track patients, record procedure parameters, and monitor outcomes. Rather than allow patient information to be housed in different places, we sequestered all medical records and imaging studies within the physical space of the Center for Image-Guided Neurosurgery at the UPMC. This center also provided working space for chart reviews and computer data entry. A prime requirement at the outset was that no chart could leave this space unless signed out to an individual and specific location.

Methods

The initial computer database system was developed by faculty in the neurosurgery department. It was created with small overhead cost and used in-house staff. An experienced physician's assistant familiar with data entry and database management was charged with maintaining and collecting all pertinent medical information. The first software used was an earlier version of dBase (dBase II, 1982; dBase LLC). Several additional software changes evolved over the next decade, with migration of the data to Paradox (Paradox/DOS 2.0, 1987; Borland Software Corp.) and different versions of dBase (dBase III, 1984; dBase III+, 1986). The database was transferred to Microsoft Access (version 7.0, 1995; Microsoft Corp.) in the early 1990s. Microsoft Access version 2007 serves as the current registry database.

Data collection has continued prospectively and systematically as new patients or new follow-up data became available. Every week the most recently treated patients are entered into the expanding database as one of the responsibilities of the physician's assistant employed by the Center for Image-Guided Neurosurgery. Once a patient has undergone GKS, the chart is given to the physician's assistant, who enters the data and then transfers the hard-copy chart to the clerical staff for filing. All patient records are kept within the department for easy access by clinical, research, administrative, and clerical staff.

The database is separated into 3 global categories of patients. The largest category (Category I) consists of brain tumors (nonschwannoma), and it currently has 6756 patients entered. In this component of the database we include our patients with functional radiosurgery indications, such as trigeminal neuralgia (currently a volume of 1239 patients). Category II consists of patients with vascular disorders, who have arteriovenous malformations, dural arteriovenous fistulas, and cavernous malformations (currently 1561 patients). Category III includes patients who have had GKS for skull base schwannomas (currently 1687 patients).

The University of Pittsburgh provides institutional

review board approval that includes a consent waiver for maintenance and use of the registry. Access to the database is provided only by an institutional review board-approved, honest broker who maintains patient confidentiality in compliance with HIPAA. The following demographic data are collected: patient medical record number, age, address, and other contact information. Previous treatment and Karnofsky score are collected as part of the general patient history. Diagnosis and anatomical site of procedure are entered. These demographic data typically serve as the initial means to locate records for specific indications prior to more extensive efforts to evaluate outcomes. Recorded procedural information includes date of the procedure, surgeon, target coordinates, lesion volume, and radiosurgical maximum and minimum doses delivered to the target(s) (Fig. 1).

To ensure 100% patient inclusion, the center's clerical staff checks the database to make sure that each chart has been entered before creating a file for it. A summary of data for each patient entered into the database is printed out and filed away as a hard copy to back up the server storage. Quality assessment is done at intervals of 6 months to check for missing data and to clean up erroneous data. This is performed by using built-in software tools that screen the data for items like abnormal dates, negative ages, duplicate names, and missing data.

Results

There have been 11,738 GKS procedures performed between August 14, 1987, and August 14, 2012, at UPMC, which is the highest-volume GKS provider in North America (personal communication; Elekta AB). Our registry can be searched by several variables but the most common method is to perform a search by diagnosis. For example, a general query of our database shows that it contains 1687 (15%) schwannomas, most of which (1566, or 93%) are vestibular schwannomas. There have been 1561 vascular malformations treated, of which 1356 (87%) are arteriovenous malformations. Other brain tumors include 866 glial neoplasms, 344 pituitary tumors, 1581 meningiomas, and 3965 brain metastases from various primary neoplasms. There have been 1239 functional procedures, of which 1088 (88%) were for trigeminal neuralgia and 131 for movement disorders.

Once a clinical hypothesis has been formulated it is presented to the physician's assistant database manager, who pulls out all of the possible information related to the research question, such as diagnosis, patient name and demographic data, year of procedure, site of procedure, and so on. This information is then exported to a Microsoft Excel spreadsheet (version 2007, Microsoft Corp.). Once it is in spreadsheet format, additional variables of interest can be inserted as columns in the spreadsheet (comorbidities, quality of life scores, MRI evaluations, procedure outcomes, and so forth).

After all of the variables of interest are added to the spreadsheet, the researcher can finish compiling the necessary information. This is typically done through a variety of methods that include chart reviews (charts are kept easily accessible and can be found by searching for the

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PATIENT INFO	First Name	Last Name	LOCATION	☐ Side (R : right, L : left)	☐ Midline	☐ Intraventricular	☐ Medulla
	Phone			☐ Frontal	☐ Basal Ganglia	☐ Intra-Orbital	
REFERRAL INFO	Address		☐ Sellar (I : intra-sellar, P : para-sellar, S : supra-sellar)	☐ Parietal	☐ Thalamus	☐ Cavernous Sinus	☐ Petroclival
	City	State	☐ Skull Base (A : anterior fossa, M : middle fossa, P : posterior fossa)	☐ Occipital	☐ Pons/Midbrain	☐ Temporal	☐ Corpus Callosum
HISTORY	Sex ☐ SSN	DOB	PRE-OP TESTING	☐ Visual Fields [A, N]	☐ Visual Acuity [A, N]	☐ Endocrine [A, N]	
	City	State	TREATMENT	☐ Surgeon (L : L. Dade Lunaford, K : Douglas Kondziolka)	☐ Volume	☐ Dose To Center	☐ Dose To Margin
DIAGNOSIS	☐ Duration of Symptoms (years)	☐ Headaches	☐ Collimators Used (mm)	☐ [4]	☐ [8]	☐ [14]	☐ [18]
	☐ Karnofsky	☐ Hemorrhage	☐ Coordinates (mm)	☐ [X]	☐ [Y]	☐ [Z]	☐ Comment
COMPLI- CATIONS	☐ # of Prior Embolizations	☐ Residual Tumor	☐ Nausea/Vomiting [A, L, B]	☐ IX-X Dysfunction [A, L, B]	☐ Death	☐ Other	
	☐ Gross Total Resection	☐ Recurrent Tumor	☐ Imbalance/Ataxia [A, L, B]	☐ New Deficit [A, L, B]	☐ Hemorrhage [A, L, B]	☐ Seizure [A, L, B]	☐ Seizure Type (G : generalized, P : partial, X : complex, partial)
FOLLOW UP	☐ Subtotal Resection (# surg)	☐ Endocrinopathy	☐ Hydrocephalus [A, L, B]	☐ New Endocrinopathy [A, L, B]	☐ Cerebral Edema [A, L, B]	☐ Radiation Necrosis [A, L, B]	☐ Headache [A, L, B]
	☐ Seizure (G : generalized, P : partial, X : complex, partial)	☐ Neuro Deficit	☐ Biopsy	☐ Brachytherapy	☐ Chemotherapy	☐ Comment	

Fig. 1. Printouts of our tumor data intake form, pages 1 and 2.

patient's last name in alphabetical order), MRI reviews, and patient contact as needed. Once all of the necessary data points have been accumulated, the researcher can import the spreadsheet into most of the common types of statistical software for advanced statistical analysis.

There are specific examples of how registry-based data have changed clinical care. For arteriovenous malformations, records of dose delivery and outcome facilitated the creation of dose-prescription guidelines. The recording of cochlear dose together with audiometry in the treatment of vestibular schwannoma led to refinement of radiosurgical planning techniques to maximize hearing preservation. Radiosurgery treatment of patients with more than 1 metastatic brain tumor was considered inappropriate before 1990. Now it is routine practice to manage disease in patients with more than 5 tumors. Further recording of brain metastases data has shown that total tumor volume is better correlated with survival than total number of tumors.

Discussion

Data derived from this computer registry has facilitated the publication of more than 400 peer-reviewed manuscripts, more than 200 book chapters, 8 books, and more than 300 published abstracts and scientific presentations. The majority of the highest-impact publications (more than 100 citations) in the field have come from

our center.³ Publications from our center are included in the neurosurgery, radiation oncology, medical physics, and neurooncology literature, but are also included in journals of broader interest such as *The New England Journal of Medicine* and *Cancer*.³

The number of publications on the topic of radiosurgery has increased dramatically over the past 3 decades. The mean number of annual publications in the field of radiosurgery has risen from 9.6 in the 1980s to 178 in the 1990s and to more than 300 in the last decade.³ The more data we have, the greater the statistical power that is available, and the higher the quality of our science. The use of radiosurgery has also increased dramatically over the past 3 decades. In 1987 fewer than 1000 patients had undergone GKS worldwide, whereas as of 2011 more than 700,000 GKS procedures had been performed, according to information obtained from the manufacturer of Gamma Knife technology (Elekta AB). A 2009 market research study done by the firm IMV projected that the use of stereotactic radiosurgery was increasing by an average of 10% per year.⁶ Much of this popular acceptance of radiosurgery can be directly correlated to the steady and growing publication of patient outcomes. A search of PubMed Central's library (www.ncbi.nlm.nih.gov) for radiosurgery publications shows the growing number of publications per year that the UPMC has released over time, thanks to our patient registry (Fig. 2). A search of our GKS registry shows the steady increase in radiosur-

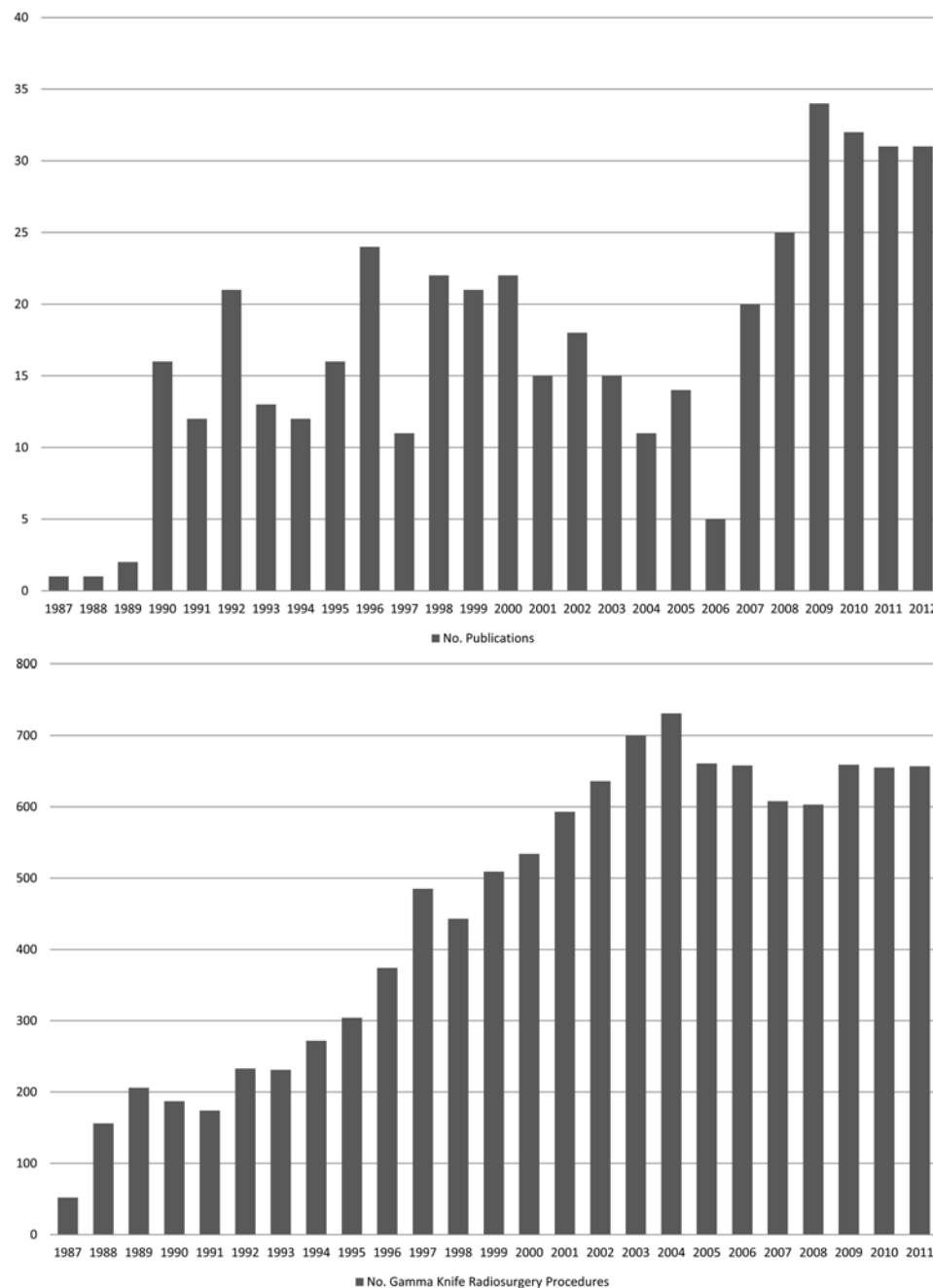


Fig. 2. Upper: Bar graph showing the number of GKS publications from data in the Pittsburgh registry over time. **Lower:** Bar graph showing the number of GKS procedures performed in Pittsburgh over time.

gery procedures that has occurred over the same time period (Fig. 2). Radiosurgery has grown from being a clinical oddity to a common procedure in centers around the world.

Challenges and Limitations

The maintenance of good-quality data is not a simple task. We have the infrastructure to keep our records in house and we use a trained clinician to collect and enter the information and to manage the database. The space and personnel constraints may be a limiting factor for less productive institutions.

To make the collection of large quantities of information feasible and useful, simplicity has been a key element in structuring the database. We have maintained broad and straightforward definitions of disease and conditions to limit the number of possible variables. We try to minimize data input that is difficult to classify. For example, we do not use free-text entries because search engines for such data are usually inadequate.

Failure to enter the data in a timely and continuous fashion would negatively impact the registry value. We use a trained clinician to input the data to have high-quality information. Nonetheless, it is difficult to collect

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more extensive information on each patient such as each follow-up, subjective symptoms, medical history, medications, allergies, family and social history, and physical examination. Although these are often very important research points, they usually need to be obtained through subsequent chart review and patient contact. This requires a specific patient medical record review and filling out required data points on Microsoft Excel spreadsheets created for a specific clinical outcome study.

Quality control needs constant vigilance. So-called fat-finger data entry errors are common and need to be cleared. Despite the regular data check made using built-in tools (as discussed above) the researcher needs to go through the spreadsheet and check for errors before performing any analysis.

Clinical research begins with a registry query but always requires a systematic review of the patients' medical records sequestered in our clinical center. In selected cases we need to follow up with direct patient contact to update information. Although it is possible to build a scientific abstract based on data accessible via the registry, an in-depth clinical article requires more detailed information obtained from the individual medical records and supplemented by review of medical images. The medical images were stored as hard-copy films between 1987 and 2003, but more recently they have been stored using digitized computer images.

General Usefulness

A physician-led database facilitates many aspects of clinical and academic life. Most physicians are required to track and log procedure statistics for various credentialing and board certifications. In our current era of evidence-based medicine and quality improvement, it is important for clinicians to take an initiative in improving their own practice as well as contributing to the overall knowledge of outcomes and disease. Clinicians can use their own data as a pilot for larger studies and grant proposals. Databases can be shared and sample sizes can swell when individual departments and clinicians merge their work. The analysis of rare problems can reach adequate sample sizes, and disparities in knowledge can be answered definitively when large, multicenter initiatives are taken. An example of this has been the creation of the North American Gamma Knife Consortium, a union of 18 academic medical centers that are interested in merging information about outcomes after GKS for rare conditions or participating in prospective clinical trials (Table 1).^{1,2,7}

The Future

As databases evolve, our current system requires continual reevaluation. Some of the ideas that we are developing for the future include a comprehensive HIPAA-compliant registry for use by one or more centers. Such a system will have more complex reporting tools and analytics. We believe this kind of data collection system will be more appropriate for multicenter use and have a broader application across different practice settings. This standard type of registry can be distributed to other centers, and it will streamline collaboration between multiple practices and specialties. Ideally, our future system will pull information from different sources and bring them together in a single research registry. We could avoid many of the roadblocks to good data collection, including the time constraint that it places on clinicians. We anticipate a single-server system that can pull demographic data from electronic medical records and pull procedure details directly from the already existing GKS software. It would even be possible to pull data from various collaborating institutions to facilitate multicenter research. In a time when technological devices are getting better at talking to each other, the amount of useful information that we can obtain by connecting various systems should be exploited.

Conclusions

We have successfully maintained a prospective electronic registry of more than 11,738 GKS procedures that were performed since August 1987. This has allowed us to analyze our outcomes, publish hundreds of scientific articles, and propel an innovative but disruptive technology into a primary role in modern neurosurgical care. The production of good-quality information is increasingly important in an era of evidence-based medicine and results-driven evaluation. We are entering an environment where the quality of a medical practice will be based on the results that its members provide. It is increasingly important that practices maintain databases of their own. The future of big-data research will rely on the integration of new database technology that can pool data from various sources and arrive at consensus results that sample from multiple institutions.

Disclosure

Drs. Lunsford and Kondziolka are consultants for Elekta AB, and Dr. Lunsford is a shareholder in Elekta AB.

Author contributions to the study and manuscript preparation

TABLE 1: Publications and studies from the North American Gamma Knife Consortium

Authors & Year	Article Title	Journal
Kano et al., 2011	Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium	<i>Neurosurgery</i>
Kano et al., 2011	Stereotactic radiosurgery for intractable cluster headache: an initial report from the North American Gamma Knife Consortium	<i>Journal of Neurosurgery</i>
Sheehan et al., 2012	Gamma Knife surgery for the management of glomus tumors: a multicenter study	<i>Journal of Neurosurgery</i>

include the following. Conception and design: Lunsford, Berkowitz, Kondziolka, Bissonette. Acquisition of data: Lunsford, Berkowitz, Bissonette. Analysis and interpretation of data: Lunsford, Berkowitz, Niranjana. Drafting the article: Lunsford, Berkowitz, Kondziolka. Critically revising the article: Lunsford, Berkowitz, Kondziolka, Bissonette, Kano. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lunsford. Statistical analysis: Berkowitz. Administrative/technical/material support: Lunsford, Kondziolka, Bissonette, Niranjana. Study supervision: Lunsford, Berkowitz, Kondziolka.

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