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Historical Perspective

The development of the international stereotactic radiosurgery society

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In this report the origins of the International Stereotactic Radiosurgery Society (ISRS) are described from the viewpoint of one of the early organizers and first president. The value of the society, the subsequent leadership, and the Jacob Fabrikant Award winners are also presented. A brief and incomplete timeline for the field of stereotactic radiosurgery is shown. The goals and mission of the ISRS continue to be met via the sponsorship of biennial meetings and publications.

Key words: stereotactic radiosurgery international stereotactic radiosurgery society (ISRS)

"The fog comes
On little cat feet
It sits looking over harbor and city
On silent haunches and then moves on."

Carl Sandburg

The field of stereotactic radiosurgery (SRS), like Carl Sandburg's *Fog,* entered the conscious awareness of the fields of neurological surgery, radiation oncology, and medical physics stealthily beginning in the mid-1980s. At that time, only a few practitioners within these fields had any clue as to the ultimate impact of this unique union of medical disciplines. In the mid-1980s, the dedicated stereotactic radiosurgical device developed by Lars Leksell, the Gamma Knife®, was in place in only three institutions in the world. The fifth Gamma Knife would not be installed in Pittsburgh until 1987. During this decade, neurosurgeons and radiation oncologists continued to study the potential use of cyclotron-generated particle beams or to use the more ubiquitous linear accelerators primarily dedicated to cancer management. Pioneers working in Buenos Aires and Paris, Italy, Boston, and Gainesville, Florida, began the conversion of existing linear accelerators to the concept of highly focused, single session radiosurgery for carefully selected patients. None of the professional organizations involved in the fields of neurosurgery or radiation oncology were interested in or possibly even aware of the impact of such technologies and their potential application to an astounding array of vascular, neoplastic, and functional disorders of the brain.

In the late 1980s, two early meetings of the nascent Leksell Gamma Knife Society occurred in Bath, England, and Charlottesville, Virginia. At these meetings it became obvious that investigators were using radiosurgery principles with a variety of technologies. I began to wonder about the value of a multidisciplinary society dedicated to scientific knowledge acquisition, independent of the technology available at each individual center. Immediately following the third meeting of the Leksell Gamma Knife Society in Pittsburgh, the first organizational meeting of the International Stereotactic Radiosurgical Society (ISRS) convened.

After these 20 years, I cannot recall, in truth, all those who participated in the ISRS start up, and certainly not all attended the organizational meeting in Pittsburgh. Multidisciplinary representation was the key. I recall that the following individuals were either present or highly supportive of forming this society. In addition to myself,

Doctors John Flickinger, Douglas Kondziolka, Jay Loeffler, Eben Alexander III, William Friedman, Frank Bova, Jack Fabrikant, Dave Larson, Robert Levy, John Buatti, and Samuel Kooy represented their centers in the United States. European representation included Doctors Christopher Lindquist, Dan Leksell, Bengt Karlsson, Lars Kihlstrom, Federico Colombo, Volker Sturm, Rita Engenhardt, Jean Regis, David Forster, Jose Samblas, and Juan Barcia-Salorio. South American representation included Carlos Carbini and Hernan Bunge from Buenos Aires. Asian representation included Tatsuya Kobayashi, Yoshihisa Kida, and Masaaki Yamamoto.

In a meeting room at the Westin William Penn Hotel in downtown Pittsburgh, the first organizational and scientific meeting of the ISRS was held. Social events followed, designed to help build the camaraderie of an organization founded by individuals from disparate academic and training backgrounds. The ISRS was conceived as a multidisciplinary society prototype. Membership and representation from the fields of neurological surgery, radiation oncology, medical physics, neuro-imaging, neurology, medical oncology, as well as allied health practitioners were envisioned as members of the organization. Then, as now, the goal was coequal representation among professionals. Turf wars- and there are still frequent skirmishes- were to be avoided.

I was elected as the first president of the ISRS and served a total of two terms of two years each, completing my leadership of the organization in 1995. During this time, the ISRS was legally incorporated as a nonprofit organization of professionals involved in the field of stereotactic radiosurgery. The ISRS remains one of the few professional organizations of its kind, based on its multidisciplinary membership. It was the first organization that monitored the continually emerging field of stereotactic radiosurgery and stereotactic body radiation therapy, methodologies now widely applied to body and spine conditions as well as brain disorders. The ISRS was designed to encourage interaction among a diverse international community of individuals working in the field. We envisioned the society to be dedicated to the advancement of SRS and related methods and to the improvement of healthcare outcomes. Among the goals was a clear desire to ensure safe application of SRS, to reduce patient morbidity associated with other alternative managements of often very difficult medical conditions, to serve as a forum for technology assessment, and to monitor this innovative practice.

The initial objectives of the IRS were summarized as:

1. To foster and encourage learning and scientific research on the topics of the brain, extracranial radiosurgery, and radiation therapy.
2. To encourage mutual fellowship, good will, and scientific collaboration between all physicians and scientists actively involved in the field of stereotactic radiosurgery.
3. To elevate and to sustain the education of all involved in the field of radiosurgery.
4. To establish and to promote high standards for the treatment of patients with radiosurgery.
5. To encourage the accurate reporting of the results of radiosurgery.

Table 1 shows the leadership evolution of the ISRS and the biennial meeting sites since its founding in Pittsburgh in 1991. The second meeting of the Society was held under the leadership of Dr. Christopher Lindquist at the Grand Hotel in Stockholm, Sweden. In 1995, the third meeting was held under the direction of Drs. Jay Loeffler and Eben Alexander, III in Boston, Massachusetts. Dr. Christopher Lindquist assumed the presidency. The fourth meeting in 1997 was held in Madrid, Spain. Dr. Jay Loeffler assumed the presidency and helped to oversee the meeting along with Dr. Robert Smee, who hosted the 1999 meeting in Sidney, Australia. The plan for the 2001 was a meeting to be held in Israel. Unfortunately it was interrupted at nearly the last minute by the onset of the Palestinian Intifada, forcing a reassignment of the meeting to Las Vegas, Nevada. Dr. Friedman was the president at that time and helped to oversee the meeting. David Larson became president in 2001 and oversaw the next international meeting in Kyoto, Japan. Dr. Larson was succeeded by Dr. Douglas Kondziolka who oversaw the meeting organized by Dr. Marc Levivier in Brussels, Belgium. A highlight of this scientific meeting was an opportunity to meet with the Queen Mother of Belgium. In 2005, Dr. Robert Smee assumed the presidency and helped to facilitate the next meeting in San Francisco, California. At that

Table 1. ISRS Timeline

Dates	Presidents	Meeting Sites	Date
1991-93	L. D. Lunsford	Stockholm	1993
1993-95	L.D. Lunsford	Boston	1995
1995-97	C. Lindquist	Madrid	1997
1997-99	J. Loeffler	Sydney	1999
1999-01	W.Friedman	Las Vegas	2001
2001-03	D. Larson	Kyoto	2003
2003-05	D. Kondziolka	Brussels	2005
2005-07	R. Smee	San Francisco	2007
2007-09	R. Spiegelman	Seoul	2009
2009-11	D. Shrieve	Paris	2011
2011-13	J. Regis	Toronto	2013

meeting, Dr. Roberto Spiegelman became president of the ISRS. His presidency culminated in the meeting in Seoul, Korea. In 2009, Dr. Dennis Shrieve became president, and the next meeting site was selected to be Paris, France. A record attendance of more than 700 individuals attended this important scientific meeting beautifully organized by Drs. Jean Regis and Marc Levivier. Dr. Jean Regis became president of the society and will serve until 2013. The 2013 meeting site was selected as Toronto, Ontario, Canada.

The reader will note that the Society more than 15 years ago made a conscious decision to alternate leadership of the society between the two medical doctor professional backgrounds, i.e. neurological surgery and radiation oncology. In the future, as other professional backgrounds emerge, perhaps the leadership rotation will be divided among members who come from other surgical, radiation oncologic, or medical physics backgrounds.

Table 2. Jacob I. Fabrikant ISRS Award Winners

Date	Awardee(s)
1995	Olof Backlund & Borje Larsson
1997	Dade Lunsford & Juan Barcia-Salorio
1999	Christer Lindquist
2001	Frank Bova, Jay Loeffler, & William Friedman
2003	John Flickinger & Tatsuya Kobayashi
2005	Federico Colombo
2007	Douglas Kondziolka & David Larson
2009	Jean Regis
2011	Masaaki Yammamoto

The Jacob Fabrikant Award

During the ISRS first 5 years, Dr. Jacob Fabrikant was increasingly recognized for his pioneering efforts related to particle beam radiosurgery and the treatment of a large number of arteriovenous malformations at the Lawrence Livermore Cyclotron Unit in Berkley, California. His neurosurgical collaborator was Dr. Gary Steinberg of Stanford University. Dr. Fabrikant's untimely death led to the Society's decision to establish an award in his honor. The Fabrikant Award was established to recognize individuals who have served as pioneers in the field of radiosurgery. The first awardees were selected at the ISRS meeting in Boston. Borje Larsson and Erik-Olof Backlund shared this initial award, which was given to them by Dr. Fabrikant's widow Irene Fabrikant, Professor Larsson's collaboration with Dr. Lars Leksell in the original development of radiosurgery beginning in 1951 was a potent stimulus to the entire development of this field. Professor Backlund, a primary disciple of Lars Leksell (and my mentor in Stockholm) was one of the most outstanding initial practitioners of Gamma Knife radiosurgery. He was instrumental in the dissemination of knowledge related to its value. Subsequent winners of the Fabrikant Award are shown in Table 2.

A Brief History of the Development of Radiosurgery

In Table 3, I present a brief but incomplete summary of the history of radiosurgery. In the late1940s, Tobias and Lawrence began working with a 340 MeV proton accelerator at the cyclotron installed at Berkley, California. The primary initial role clinically (beginning in 1954) was for patients with pituitary tumors and cancer pain caused by hormone sensitive tumors. In such patients pain could be improved by radiosurgical ablation of the pituitary gland. Lars Leksell was aware of this early work, having done a stereotactic surgery fellowship with Ernst Spiegel and Henry Wycis at Temple University in Philadelphia in 1947. Leksell returned to Stockholm and by 1949 had published a landmark article that described his first stereotactic guiding device. In 1951, he coined the term stereotactic radiosurgery. He began to collaborate with Borje Larsson in the use of cross-fired protons from a 185 MeV cyclotronic accelerator in Uppsala, Sweden. He also was a pioneer in the combination of imaging technologies with therapeutic guiding devices, such as ultrasound and encephalography. He even used 200 kV x-rays to treat both trigeminal neuralgia and selected behavioral disorders.

Leksell's initial clinical work using cross-fired protons was logistically difficult because of the need to transport patients from Stockholm to Uppsala. Larsson and Leksell envisioned the creation of a dedicated radiosurgical device that could be housed in the routine hospital environment. In 1967, they arranged for the construction of the first prototype Gamma Knife (Unit I). The first two patients were treated at the manufacturing site (Studsvik, Sweden), prior to moving the cobalt-loaded unit to a private hospital, the Sophiahemmet, in Stockholm. The first Gamma Knife had 179 cobalt sources arranged in a hemisphere array, focused on a target point within the brain. There were 127 patients treated in the first eight years. The potential role of the Gamma Knife for nonfunctional disorders including arteriovenous malformations and acoustic neuromas was discussed with Leksell. A number of the initial

Table 3. A Brief History of Radiosurgery Pioneers

Date	Pioneer(s)	Technology and Location
1947	Lawrence & Tobias	Proposed Protons, Berkeley California
1949	Leksell	Stereotactic Head Frame, Stockholm
1951	Leksell	Coins Term Stereotactic Radiosurgery
1951-60	Leksell	Orthovoltage Xrays, Ultrasound, Lund
1954	Tobias et al.	Charged Particle Treatment, Berkeley
1960s	Leksell & Larsson	Protons, Uppsala
1967	Leksell	Prototype Gamma Knife (Unit 1)
1968-	Kjellberg	Protons, Boston
1975	Leksell	Gamma Unit 2 (redesigned)
1982	Barcia- Salorio	Linac, Madrid
1983	Forster	Gamma Unit 3, Sheffield
	Bunge	Gamma Unit 4, Buenos Aires
1984	Betti & Derechinksy	Linac, Paris & Buenos Aires
1985	Colombo	Linac, Vicenza
1987	Lunsford	Gamma Unit 5, Pittsburgh
1988	Podgorsak & Olivier	Linac, Montreal
1988	Friedman, Buatti, Bova	Linac, Gainesville
1988	Winston, Lutz, Alexander, & Loeffer	Linac, Boston
1990s	Fabrikant,Levy, & Steinberg	Helium Ion, Berkeley
1994	Adler	Cyberknife, Palo Alto

pioneers in radiosurgery in Stockholm worked with Leksell, especially after the construction of the second Gamma Knife in 1975. This unit was placed in the basement of the Radiumhemmet at the Karolinska Hospital in Stockholm. Ladislau Steiner, Georg Noren, Erik-Olof Backlund, and Tiit Rahn were amount the initial primary users of the Gamma Knife for vascular malformations and tumors.

By 1983, two disciples of Leksell, Hernan Bunge and David Forster persuaded the reluctant Leksell to authorize the construction of two additional prototype gamma units. Gamma Knife 3 went to Sheffield, England, under the direction of Dr. Forster, and Gamma Knife 4 went to Buenos Aires under the direction of Dr. Bunge. The original proposed modification of this unit proved to be far in advance of the technologies then available. Leksell and Larsson's concept was that the bed should be robotically moved so that the patient target could be centered within the focus of the x-ray beams generated by the Gamma Knife. The focus was fixed. Unfortunately, this concept (a vision of what eventually became the Perfexion® device 20 years later) could not be successfully engineered. The units had to be reengineered at the manufacturing site in Switzerland before reentering clinical implementation at the above sites.

It was at approximately the same time that Doctors Betti and Derechinsky began to collaborate in Paris and in Buenos Aires using a modified linear accelerator for radiosurgical treatment, primarily for vascular malformations. In the mid-1980s, the team of Friedman, Bova, and Buatti developed a system using a modified linear accelerator at Gainesville, Florida. Four pioneering investigators working in Boston (Ken Winston, Wendel Lutz, Jay Loeffler, and Eban Alexander) began to use a modified linear accelerator in Boston. Federico Colombo also began to use a modified LINAC in Vincenza, Italy, and Juan Barcia-Salorio began to use linac radiosurgery in Madrid.

During the early 1980's the financial and regulatory approval for establishment of the next generation Gamma Knife (#5) was completed in Pittsburgh. The unit entered clinical operation in Pittsburgh in 1987. The first patients treated had acoustic neuromas and AVMs. The potential ability to expand the range and usefulness and accuracy of linear accelerator radiosurgery was explored by John Adler, who developed the

unique combination of a linear accelerator mounted on an industrial robotic arm (the CyberKnife®).

By this time, the "gentle fog" of radiosurgery had exploded upon the worldwide medical community, and its potential role first in the brain and subsequently its potential use in other areas of the body and spine became clearer. The evolution in technologies for Gamma Knife went hand-in-hand with the evolution of superior quality brain and body imaging. Computed Tomography (CT) became integrated in the late 1970's and magnetic resonance imaging (MRI) in the early 1990's. The resolution, quality, and reliability of these imaging tools greatly expanded the indications and potential role of radiosurgery. Tumors could be detected before disease processes became far advanced. Older or medically infirm patients with significant patient comorbidities required lesser invasive management strategies that matched the advances in diagnostic imaging. Radiosurgery became mainstream during the decade of 2000-2010. At various centers, radiosurgery began to be a preferred primary management for selected indications such as acoustic neuroma (Fig 1). This had a profound impact on training programs. Oversight committees such as the American Board of Neurological Surgery began to require that radiosurgical education was included in the education of trainees in Neurosurgery.

The clinical indications for radiosurgery continue to expand. AVMs became better delineated using multidimensional MRI, digital-subtraction angiography, and 2D and 3D angiography. Acoustic neuromas previously targeted using CT or CT cisternography were better defined using high definition MRI. SRS became a common strategy for management of meningiomas, especially those located in critical structures of the skull base. The initial use of Gamma Knife in movement disorders or behavioral disorders began to gain renewed momentum despite the push for deep brain stimulation techniques. While radiosurgery had no initial role envisioned as an alternative for treatment of common conditions such as metastatic cancer, it soon became the #1 indication worldwide. In addition, emerging roles in epilepsy and in glioma management soared.

In more recent years, the evolution of brain radiosurgery has stimulated the potential application to both body and spine radiosurgery. Linear accelerator-based technologies facilitate treatment of lung cancers, bone cancers, as well as abdominal and liver tumors. The technological means to reduce target motion was critical, and those methods have continued to develop based on real time or fiducial tracking.

ISRS Congresses

The topics evaluated by the ISRS congresses include:

1. SRS versus stereotactic radiation therapy (SRT) versus conventional fractionated radiation therapy
2. Outcomes of benign and malignant tumors, functional disorders, and vascular malformations.

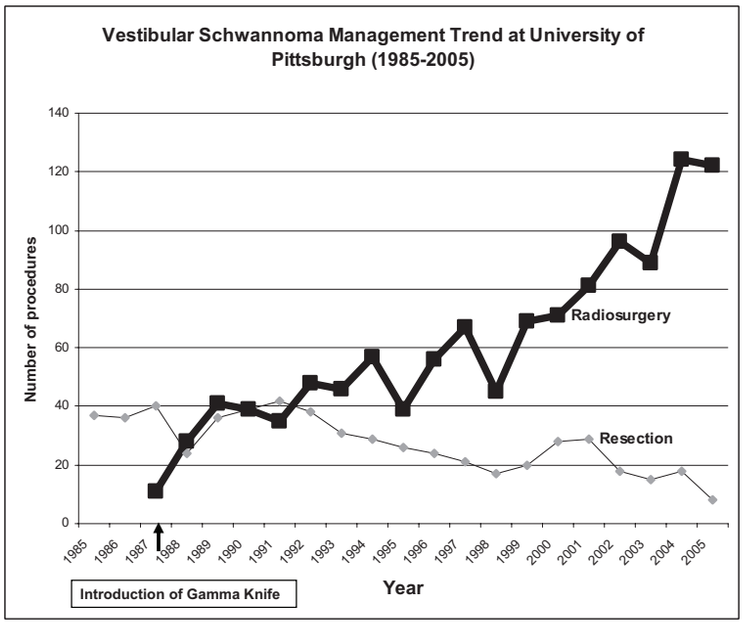

Figure 1. The effect of SRS on the management of acoustic neuroma at the University of Pittsburgh Medical Center, Presbyterian Hospital over 20 years.

3. Complication management.
4. Radiobiology and experimental SRS.
5. Technology and imaging evolution.
6. Cost effectiveness.
7. Treatment planning.

The decades of development of the field of radiosurgery are shown in Table 4. The 1950s saw invention; the 1960's, further collaboration among multidisciplinary individuals; the 1970s, the early clinical applications; the 1980s, consolidation and further refinement of the technologies; 1990s, worldwide expansion and explosion of the field of radiosurgery. During the first decade of the new millennium (2000-2010) the application of radiosurgery as initial management for a wide variety of malignant brain tumors, spinal and extracranial radiosurgery, and an increasing role of functional radiosurgery. The decade of 2010 -2020 will likely see further technological development of new directions in the field of radiosurgery as it is applied to brain, spine, and body indications.

The ISRS Educational Mission

The efforts of the ISRS have been helpful to the worldwide understanding of the potential value and role of radiosurgery as a mainstream treatment methodology. The original goal of the Society- to facilitate scientific communication among individuals with different training backgrounds -has been fulfilled. Summaries of the papers given at individual congresses were undertaken by a number of individuals. Dr. Douglas Kondziolka was the overall managing editor of the initial volumes of *Radiosurgery* published by Karger. He was assisted by a number of individual volume editors. The Society has more recently decided to pursue a peer-reviewed publication, *Journal of Radiosurgery and SBRT*, under the direction of Dr. Samuel Ryu. The current issue represents the second issue of this important activity. This important educational mission of the ISRS has clearly been achieved. Table 5 shows the list of topics of the >5000 published articles related to SRS. Eighty-four articles have more than 100 citations in the literature.

Concluding Thoughts

Future efforts of the Society likely will include additional publications and sponsorship of the biennial meeting, where the most recent advances are reported. I personally hope that the ISRS will stimulate participation in clinical trials, consider underwriting a training fellowship for qualified individuals, and continue to pursue the exchange of scientific knowledge at the biennial meetings and in the new peer reviewed journal.

As noted in the ISRS website, "As the field of radiosurgery continues to develop with increased study, research and new technologies, the aim of the ISRS is to broaden the scope of this unique international forum and to gather a large audience" of individuals interested in brain, spine, and body radiosurgery and related topics during the biennial meetings. The Society continues to be an example of how multidisciplinary collaboration can enhance the outcome of our patients.

Table 4. Major Events in the Field of Stereotactic Radiosurgery

Decade	Phase	Major Developments
1950s	Invention	Leksell Defines the Field; exploration of radiosurgery tools (photons vs particles)
1960s	Collaboration	First Collaboration between surgeons, radiobiologists, oncologists; Gamma knife and particle beams
1970s	Early Development	Clinical Applications of Gamma knife and protons
1980s	Refinement	Linac Adaptations; Gamma knife redesign
1990s	Expansion	World wide explosion; roles for AVM and tumors established; application to cancer
2000s	New Directions	Stereotactic spine and body SRS advances
2010s	Consolidation	Major role as alternative to microsurgery or radiation therapy technologies

Table 5. The Literature Explosion Related to Stereotactic Radiosurgery (1951-2011 > 5000 published articles)

Topics with > 100 Citations	
Clinical Diagnoses	
Brain Metastasis	20
AVM	17
Acoustic Neuroma	9
Meningioma	8
Trigeminal Neuralgia	5
Glioma	2
Spinal SRS	2
Pain Management	1
Cavernous Malformation	1
Lung Cancer	1
Technology	
Linac Modification	4
Cyberknife	2
Gamma Knife	1
Other	2
Physics/Radiobiology	
Dose/response	6
Quality Assurance	3
TOTAL	84

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