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TOPIC REVIEW

The evolution of stereotactic radiosurgery in neurosurgical practice

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Abstract

Introduction Stereotactic radiosurgery (SRS) was born in an attempt to treat complex intracranial pathologies in a fashion whereby open surgery would create unnecessary or excessive risk. To create this innovation, it was necessary to harness advances in other fields such as engineering, physics, radiology, and computer science.

Methods We review the history of SRS to provide context to today's current state, as well as guide future advancement in the field.

Results Since time of Lars Leksell, the young Swedish neurosurgeon who pioneered the development of the SRS, the collegial and essential partnership between neurosurgeons, radiation oncologists and physicists has given rise to radiosurgery as a prominent and successful tool in neurosurgical practice.

Conclusion We examine how neurosurgeons have helped foster the SRS evolution and how this evolution has impacted neurosurgical practice as well as that of radiation oncology and neuro-oncology.

Keywords Neurosurgery · Stereotactic radiosurgery · History · Lars leksell · Gamma knife

Introduction

The evolution of stereotactic radiosurgery (SRS) illustrates the history of a disruptive technology. Since its origins, when some radiation oncologists maintained a reluctance to its introduction into neurosurgical practice, as well as reluctance by some neurosurgeons to accept this introduction into their own practice, it has dramatically evolved and subsequently improved in safety and effectiveness. Now SRS represents a well-established therapeutic modality in the management of central nervous system (CNS) disorders seeded in difficult-to-treat locations or for patients that are poor candidates to open surgery. Stereotactic radiosurgery derived from important diagnostic and therapeutic advances in other fields of medicine, such as the discovery of X-rays by Roentgen in 1895 and the development of stereotaxis at the beginning of the 1900s [1, 2]. Furthermore, dramatic advances in neuro-imaging in the 1960s to the 1980s allowed for the development of current SRS technologies [3, 4].

Recently, it was clear that the accelerated evolution of radiosurgical and radiotherapeutic techniques demanded a formal reevaluation of concepts. For this reason, the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) formed the Stereotactic Radiosurgery Task Force, which together with the American Society for Radiation Oncology (ASTRO) met in March 2006 to formally define SRS, taking into account its historical, current, and potential future applications. Consensus subsequently defined Stereotactic radiosurgery as the use of externally-generated ionizing radiation (IR) to eradicate or inactivate a specific target within the brain or spine [5]. Moreover, the precision of the delivered IR must rely on a rigidly attached stereotactic frame, other immobilization system and/or stereotactic image-guidance technology. Although more commonly performed during a single session, up to 5 sessions can be used with the purpose

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of further reduction in injury to surrounding normal tissue through fractionation without compromising its therapeutic potential [5].

Over time, refinements in SRS occurred in such a way that a collegial partnership between neurosurgeons, radiation oncologists, and physicists was critical in assuring the best possible patient care. The essential, multidisciplinary nature of the team performing SRS was recognized by the Stereotactic Radiosurgery Task Force and ASTRO which together with the American College of Radiology (ACR) designed specific responsibilities to the individual members of this multidisciplinary team [6]. Such a multi-disciplinary framework creates multiple advantages. First, patients are counseled from a variety of perspectives on the available treatment options and risks. Second, a team approach optimizes the safety and therapeutic effectiveness of stereotactic radiosurgery.

Inception of radiosurgery

Stereotactic Radiosurgery was developed by the Swedish neurosurgeon Lars Leksell, who in 1951 published his seminal paper where he coined the term *radiosurgery* for the very first time [7, 8]. However, previous scientific milestones were necessary to create the technology critical for SRS. The modern era of stereotaxis arose when the pioneer of British neurosurgery, Victor Horsley, and Robert Henry Clarke developed a Cartesian tricoordinate system to target cerebellar nuclei in monkeys; their work describing the use of the first stereotactic apparatus was published in 1908 [1]. Only 10 years later, Aubrey T. Mussen redesigned the device for human applications [9]. However, no neurosurgeon would be willing to take the risk of treating patients based on merely external skull landmarks [10]. With the development of the X-rays and plain-film radiography, the neurologist Spiegel and the neurosurgeon Wycis from Temple University were the first to correlate stereotaxis with intracranial landmarks-such as the calcified pineal gland or the anterior commissure—and to publish on the clinical application of stereotactic neurosurgery for neuropsychiatric conditions in 1947 [11, 12].

Lars Leksell combined stereotaxis and radiation in an attempt to develop an alternative method to treat neurological disorders while avoiding the morbidity associated with open surgery of the time. Open surgery was associated with a rate of morbidity as high as 60% even in the hands of his mentor Herbert Olivecrona, who had trained with Harvey Cushing in the United States and later became known as the father of Swedish Neurosurgery [13]. Leksell designed a novel and simpler center of arc based stereotactic frame in 1949 [14] and subsequently described his ideas and concepts regarding the first stereotactic irradiator in his landmark paper of 1951 [7]. In collaboration with the department of physics at the Karolinska Institute, Leksell was able to materialize the first-in-human radiosurgery procedures in 1953. He treated patients with trigeminal neuralgia and psychiatric conditions by coupling an orthovoltage X-ray tube to his previously described stereotactic frame [15]. The next technological improvement was the use of the Uppsala University cyclotron to deliver plateau high-energy proton irradiation rather than low-energy X-rays in 1960. This technique was later abandoned after it proved too cumbersome and expensive for routine clinical use [16]. Nonetheless, through this experience a new partnership with the physicist and radiobiologist Börje Larsson was born and allowed the evaluation of the first-generation linear accelerator (LINAC)-based SRS procedures. Unfortunately; they found it too imprecise to be adopted into clinical practice at that time [17].

Later, Leksell's team envisioned the use of Co-60 as source of high energy photons (i.e. gamma rays), which led them to build the first Gamma Knife (GK; Elekta AB, Stockholm Sweden) unit between 1963 and 1968. Imaging target localization was initially based on X-ray films, but the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) into the Karolinska Hospital, in 1974 and 1980 respectively, fostered the adaptation of the stereotactic technique to these new technologies [3, 4].

The next milestone in the history of the GK was its establishment in United States. Dade Lunsford spent one month during his neurosurgery residency with Leksell in 1979 and then returned to the Karolinska Institute for a year after graduation as the recipient of the AANS Van Wagenen Fellowship Award (1980–1981). Subsequently, he returned to Pittsburgh, Pennsylvania to develop and refine CT-compatible technologies in radiosurgery. Under his leadership, the installation of the GK unit at the University of Pittsburgh in August 1987 heralded an explosion of scientific literature that made the case for the use of radiosurgery as an essential therapeutic modality in the neurosurgical armamentarium. Since then, new versions of the Leksell Gamma Knife have been developed at regular intervals to its modern form (Fig. 1).

In parallel to the development of the Gamma Knife, two additional radiosurgery platforms emerged for use in neurosurgical practice (Fig. 2). The evolution of proton and LINAC-based radiosurgery benefited from the momentum gathered by the research on particle physics during the Second World War (1939–1945). The Nobel laureated physicist, Ernest O. Lawrence invented the 60-inch cyclotron at UC Berkeley in 1929, which represented the first particle accelerator where heavy particles could be accelerated in a non-linear fashion (i.e. circular) [18]. Theoretical and practical advances in this field during the war period opened the possibility of using protons for clinical purposes, as initially suggested by the physicist Robert Wilson from Harvard

Fig. 1 The Gamma Knife Icon platform, with on-board cone-beam computed tomography and frameless radiosurgery capability

University in 1946 [19]. The novel high-energy 184-inch synchrocyclotron (the modified calutron used during the war to purify U235) at Lawrence Berkeley Laboratory allowed the delivery of the first proton-based radiation therapy to a pituitary patient in 1952 [20]. However, the first procedures applying the therapeutic concept of the Bragg peak were not performed until later in the 1960s at the Gustav Werner Institute in Uppsala (Sweden) and the Harvard Cyclotron Laboratory [18]. Kjellberg, a Massachusetts General Hospital neurosurgeon, described his experiences with Bragg peak proton therapy in patients with pituitary adenomas and arteriovenous malformations [21, 22]. The Kjellberg's isoeffective risk centile curves were based on data from a modest number of AVM patients treated with proton therapy in his initial experience, however they pioneered the development of more modern dose–effect curves for radiation necrosis of the brain [21, 23–25]. This concept was the basis for future advanced dosimetry seen in Gamma Knife and LINAC-based SRS. Further advances in imaging technologies (i.e. CT and MRI) allowed the acquisition of tissue-density information which was required for better dose calculations and treatment accuracy [19]. Additionally, they also fostered improvements in patient positioning systems. The first hospital-based facility was established in Loma Linda Medical Center in 1990 and after this, the acceptance of proton-based SRS would allow this technology to evolve and spread.

Another milestone in the history of SRS was the invention of the klystron, the first LINAC prototype able to produce MeV X-rays [26]. This invention happened in the context of the Second World War, in an attempt to create better radar systems. Although klystrons are based on the principle of *velocity modulation*, which was first reported in Germany in 1935 [27, 28],it was not until the Varian brothers joined the laboratory of Dr. William Hansen, Professor of Physics at Stanford, that the klystron was developed as reported in 1939 [29]. Russel Varian was a physicist working on private communication technologies and Sigurd Varian was a commercial pilot concerned about airspace security. Hansen had invented the cavity resonator or rhumbatron (an essential component of the klystron, analog to the magnet coils developed by E. Lawrence to create magnetic fields) and the theory to use this rhumbatron as an element of a bigger circuit [26]. Eventually, the group would take less than two years to create the klystron.

The Varian brothers would patent this technology and, together with Willian Hansen, funded what later would become Varian Medical Systems (Palo Alto, CA). Even when the first clinical LINAC-based conventional radiotherapy units appeared in England during 1953 and 1954 [30], this technology gained major clinical relevance after the Stanford radiologist Henry S. Kaplan treated the first patient in US in 1956 [31]. After GK and proton-based irradiation had slowly demonstrated the utility of SRS, Neurosurgeons Federico Colombo from Italy and Osvaldo Betti from Argentina took the lead in developing LINAC-based SRS [32–34]. Lutz and Winston later developed the dosimetry of this method [35], improving LINAC-based SRS and allowing extracranial applications of radiosurgery (Fig. 3).

Initially, LINAC-based SRS required rigid immobilization of the patient's head to achieve maximum accuracy. It would be the Stanford neurosurgeon John Adler who, in collaboration with the Stanford School of Engineering, developed an efficient computer algorithm to correlate X-rays and CT scans in real time [26]. Adler had spent time working with Leksell and wanted to apply radiosurgical principles to targets in the body and not just the brain. The miniaturization of the LINAC by the end of 1980s allowed the coupling of a LINAC to industrial robotic arms. Now, this system could use real time patient position/motion information to correct LINAC irradiation with submillimeter accuracy. This represented the origin of the frameless and non-isocentric SRS which are features of the next technology released in 1991, the CyberKnife (Accuracy Inc., Sunnyvale, CA), a new platform that ultimately extended the reach of radiosurgery outside the CNS. To this day, Dr. Adler has continued to refine radiosurgical technology as highlighted by his help to develop the new Zap system [36].

Radiosurgery's evolution

Radiosurgery evolved on the basis of Leksell's stereotactic model, where radiation could be delivered from any point of an arc external to the cranium, towards a centered target known as isocenter, a point in space where all beamlets converge and sum intensity. The goal of SRS, regardless of its different modalities, is to create a steep dose gradient

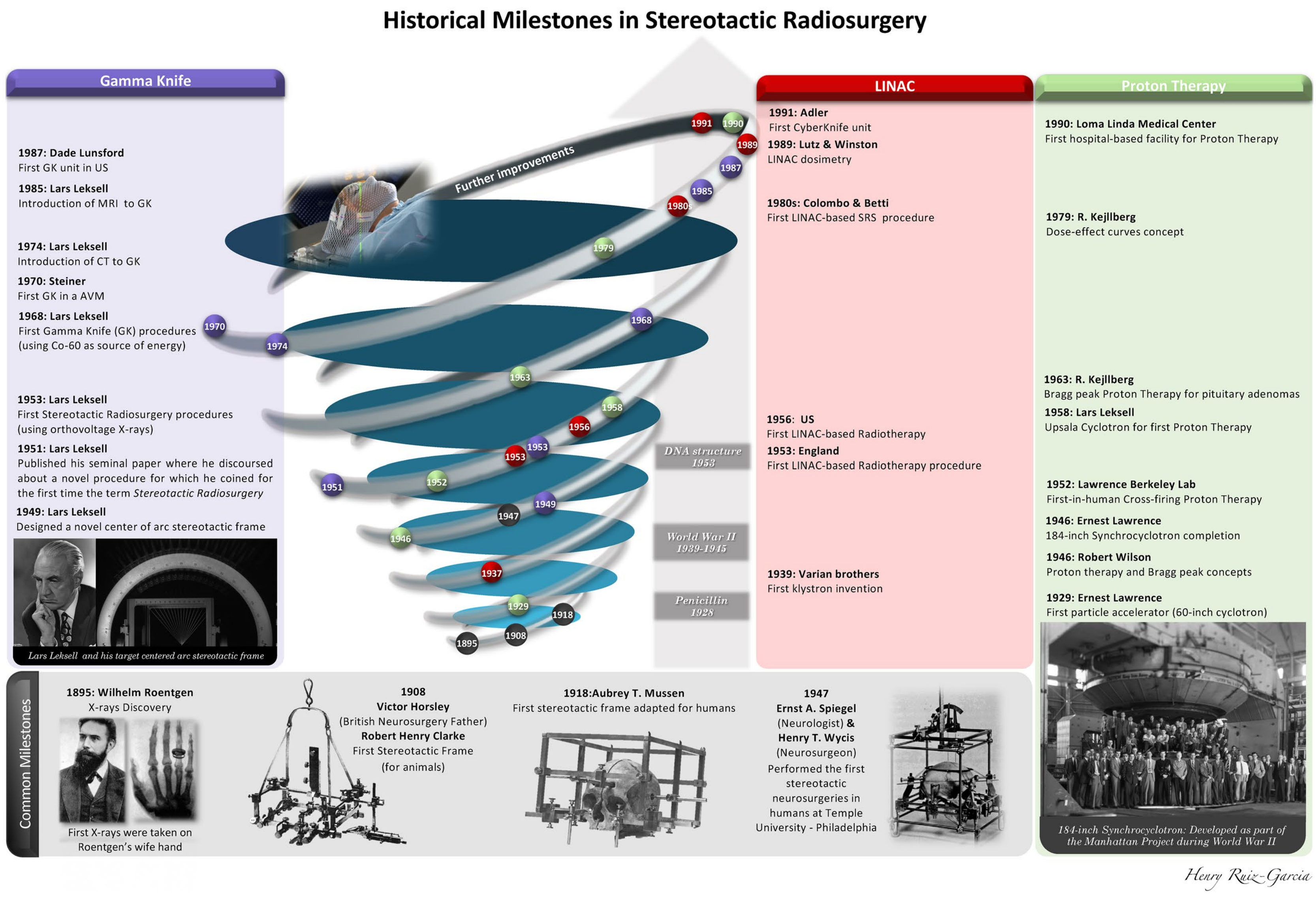

Fig. 2 Historical milestones in stereotactic radiosurgery

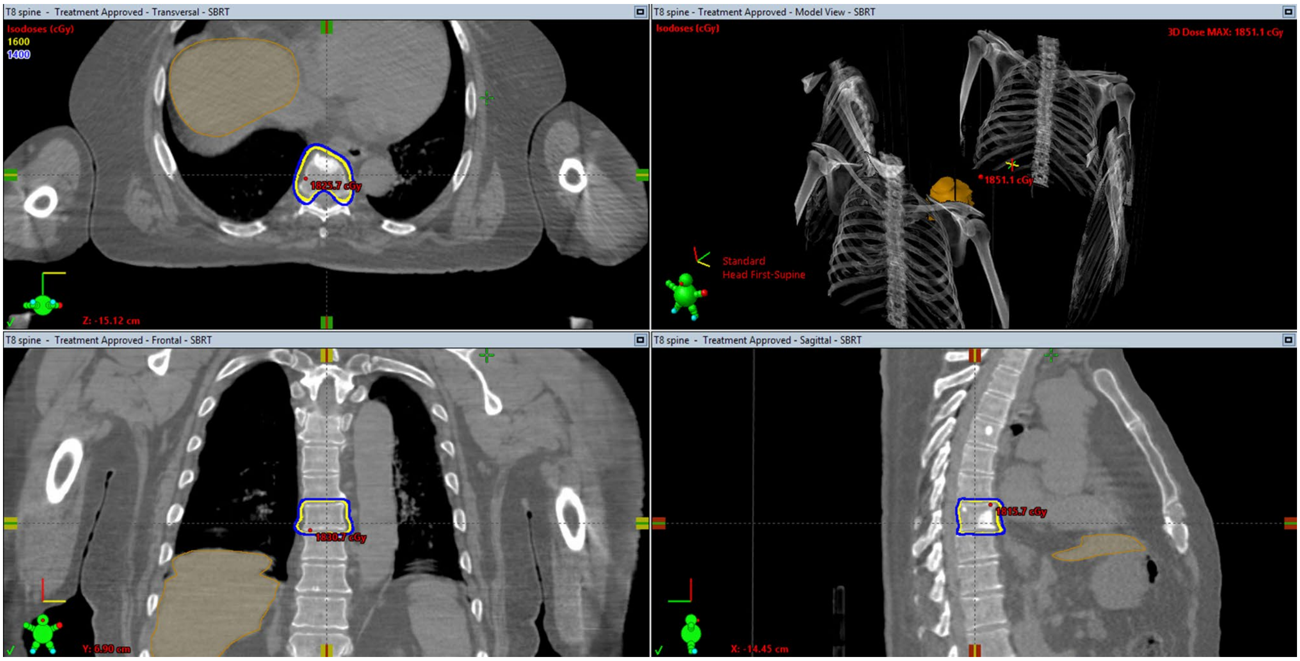

Fig. 3 Dosimetric image of a linear accelerator-based spinal radiosurgery plan for a metastatic lesion

for allowing the distribution of a high radiation dose to the targeted lesion while avoiding damage to the normal brain parenchyma. Freedom gathered from the robotic arm of CyberKnife allowed this technology an optional non-isocentric delivery, while GK and LINAC-based SRS still relied solely on isocentric irradiation. The shape of the beam can be generated through circular cones (i.e. in GK procedures) or micro-multileaf collimators-MLC (i.e. in LINAC-based procedures) that allow the beam to take the shape of tumor's cross-sectional area orthogonal to the beam axis. If the lesion is complex in shape, more than one isocenter can be used at the same time in GK procedures, which is referred sometimes as "packing".

The development of faster computers allowed the use of accurate calculation algorithms to generate more rapid planning and more accurate dose distributions [37]. Similarly, the development of CT and MRI allowed the acquisition of better information about tissue location and density which are key variables in radiosurgical targeting and dosimetric calculations [19]. Additionally, these new imaging modalities have allowed more precise and accurate target localization and delineation. Faster computers also allowed the development of "inverse planning" techniques where dosimetric goals (e.g. target dose, critical structure constraints, conformality, etc.) are set first, and then a computer program optimizes parameters (beam energy, fluency, direction, etc.) to achieve the desired dosimetric goals.

Delivery systems have also evolved in order to increase safety profile of SRS, the most recent is the development of volume-modulated arch therapy (VMAT) [38] which is a combination of fixed-beam intensity modulated radiation therapy-IMRT (fixed beams are static radiation beams delivered only from certain angles of the arc in order to spare radiation of critical structures) and conformal arc techniques (the beam is spun around the patient to allow for a continuously shaped beam to match the beam-eye-view area of the target at all delivery angles) (Fig. 4). VMAT also offers the possibility of treating multiple targets with only one isocenter, drastically decreasing treatment duration [38].

Another technical advance is image-guided radiation therapy (IGRT). Although SRS has traditionally used stereotactic frames to localize the target and immobilize the patient, image guidance has facilitated the use of noninvasive frameless immobilization, and consequently multiple session treatments. IGRT is a generic term which infers the use of orthogonal X-rays, CT scans, optical guidance, and/or MRI guidance to allow for verification of the correct patient position immediately preceding irradiation. With a CT scan immediately preceding SRS, subtle adjustments in patient positioning can be achieved to allow for correct patient positioning during SRS, which remarkably improve accuracy.

Impact of radiosurgery

While initially stereotactic radiosurgery was envisioned to be used in the treatment of functional neurosurgical conditions such as cancer related pain, trigeminal neuralgia, psychiatric

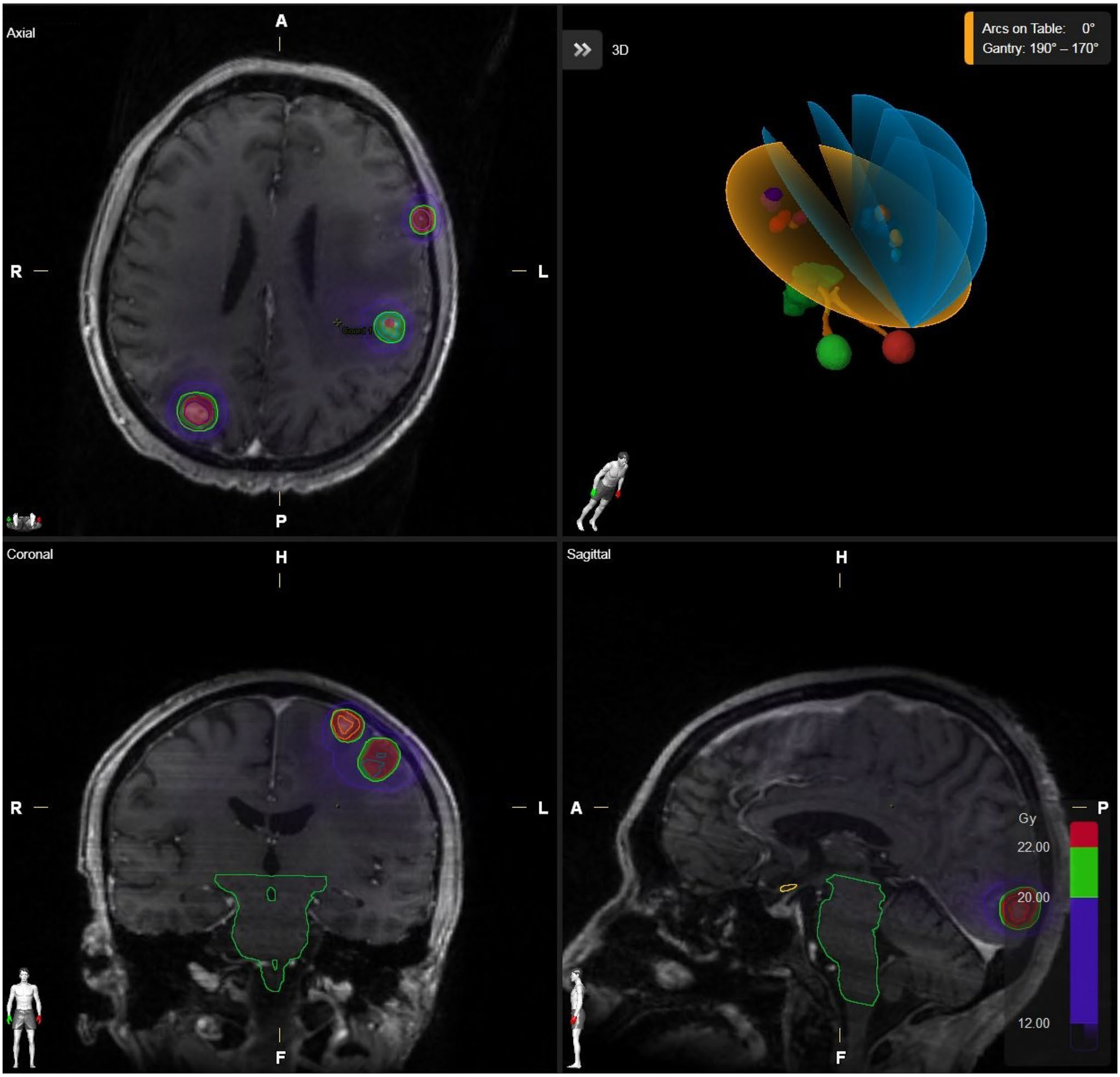

Fig. 4 Dosimetric image of a single-isocentric volumetric modulated arc-based therapy treatment plan for brain metastases

conditions, and movement disorders, SRS promptly arose and is now used most frequently as a therapeutic tool for the treatment of tumor pathologies. Given the lack of computed-imaging at the beginnings of the radiosurgery history, pituitary adenomas and AVMs were the main focus of research and clinical practice. Pituitary adenomas were easy to indirectly localize inside the sella turcica using plain X-rays and angiograms allowed the biplanar targeting of vascular pathologies such as AVMs [39]. Further refinements in SRS technology led to its exponential increase in the number of procedures for treatment of several pathologies. According to data from the GK manufacturer (Elekta AB, Stockholm, Sweden) more than 1 million patients were treated with GKRS. Additionally, annual incidence of patients receiving radiosurgery (LINAC-SRS plus GK-SRS) is more than 75,000, with an annual increased projection of 10% [40, 41].

Currently, the top 5 most common indications for SRS are: brain and spine metastases, trigeminal neuralgia, meningiomas, schwannomas and AVMs [42, 43]. While not originally designed for this purpose, the role of SRS for metastatic brain disease has grown appreciably in the last years, and it can be indicated as adjuvant to conventional radiotherapy or open surgery. Moreover, the list of patients considered appropriate for SRS continues to grow, with

Yamamoto et al. supporting SRS as treatment in selected patients with up to 10 brain metastases [44]. Radiosurgery also continues to extend its reach to others conditions, as is evident from recent reports supporting a role in involuntary movements [42, 45].

Future of radiosurgery

Despite the importance that radiosurgery has gained in the management of neurosurgical patients, several studies have come to identify significant gaps in neurosurgical residency education. A survey from AANS showed that two-thirds of the residents attending a AANS-sponsored SRS conference did not receive formal training in radiosurgery even when 79% planned to perform the procedure in the future [46]. Confidence with required skills to perform SRS, as well as training satisfaction, follows the same mournful trend in other studies as well [43]. Interestingly, an opposite trend was found when radiation oncologist residents were surveyed [47]. If anything, this would suggest that a training gap extends across specialties.

The advantages of a multidisciplinary collaboration in obtaining improved patient outcomes in radiosurgery have been evident through its history and evolution. Radiation oncologists play an important role, as supported by ASTRO/ACR guidelines [48], and offer the potential to enhance SRS skills and knowledge in neurosurgery residents, but there is a need for improved SRS integration within the neurosurgical team through daily clinical activities, joint conferences and courses, fellowships, among others. Radiosurgery spans all sections of neurosurgery: tumor, spine, functional and stereotactic, pediatric, and vascular. This underscores the prominence that radiosurgery has gained in the field of neurosurgery and the value that neurosurgeons add to radiosurgical care. The intimate relationship between radiosurgery delivery, neurosurgical resection, endovascular techniques, radiosurgical toxicity, and stereotaxy cannot be underestimated. As advancements in SRS patient selection, planning, and delivery continue into the future, neurosurgery will have a critical role to play. As such, SRS scholarly programs that are included as a formal component in the curricula of neurosurgery residents appears as the logical next step to take in Neurosurgical education.

SRS also has planned and will likely see expanded functional indications. These include the management of movement disorders such as essential tremor and for epilepsy in some cases such as those with hypothalamic hamartomas [49, 50]. There is also the potential for SRS to play an expanded role in the management of patients with severe and intractable obsessive compulsive disorder [51]. While these indications go beyond those typical for a neuro-oncology audience, neurosurgeons will play an essential role in the investigation, application, and refinement of SRS for these indications.

Contemporary and future applications of SRS are not limited to the aforementioned. The American Society for Radiation Oncology (ASTRO) has already published a general guideline to maximize the potential benefits of combining radiation with molecular targeting or immunomodulatory agents [52]. In this regard, active investigation is being carried out on SRS as a potentiator of different treatments through its capacity to modulate tumor immune dynamic and cancer cells profile in gliomas and brain metastases. To date, several preclinical and clinical studies have suggested that SRS could synergize with immunotherapy and cell therapy [53–55]. Appropriate radiation delivery modality, dose, fractionation and timing are crucial factors to success in this purpose as SRS could differentially influence tumor biology and therapeutic efficacy depending on how these factors variate [55–57].

Conclusion

Radiosurgery has made profound changes in the care of neurosurgical patients with complex intracranial and/or spinal pathologies. Neurosurgeons have been instrumental in the inception, innovations, and refinements of SRS; and nowadays play a crucial role in the multidisciplinary partnership that selects, treats, and manages radiosurgery patients. Neurosurgeons also must ensure adequate training and education of future generations. The safety and efficacy of SRS has been demonstrated across a wide variety of neuro-oncology indications; the refinements in SRS will likely lead to further advancements and improved care in ways that we cannot yet imagine.

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Compliance with ethical standards

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Research involving human and/or animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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