Review Article

pISSN 1738-6217 • eISSN 2765-6608

J Korean Stereotact Neurosurg 2021;17(1):6-13
<https://doi.org/10.52662/jksfn.2021.00038>

Received: May 25, 2021

Accepted: June 9, 2021

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ORCID: <https://orcid.org/0000-0002-6568-1009>The mixed era of stereotactic
radiosurgery and radiotherapy

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Through advances in radiotherapeutic techniques, the accurate and precise delivery of large, highly conformal doses of radiation has become more common in stereotactic radiosurgery (SRS). The increased accuracy and reliability of radiotherapy (RT) have also led to a change from traditional RT hypofractionated RT when conducting high-dose irradiation. The mixed era of RT and radiosurgery has caused confusion for many physicians who treat patients receiving radiation. This review briefly touches on the definitions and indications of RT and SRS based on radiobiology and radiophysics.

KEY WORDS: Radiosurgery, Radiotherapy, High-energy radiotherapy

INTRODUCTION

Since the introduction of radiosurgery by Leksell in 1951 [1], stereotactic radiosurgery (SRS) with delivery of a high dose of radiation in a single session has been used for the treatment of lesions in the brain and spine [2]. He developed the first commercially available dedicated radiosurgical device called the “Gamma Knife” (GK) in 1968. This machine made it possible to precisely deliver a single, large dose of highly conformal radiation to any number of intracranial sites using 201 fixed cobalt sources aimed at a center point. Since he coined the term “stereotactic radiosurgery”, 330 centers of GK radiosurgery in 54 countries currently treat a total of 80,000 new patients each year. Through approximately 70 years of SRS experience that began with GK radiosurgery, the role of radiosurgery has expanded to a wide variety of benign brain tumors, arteriovenous malformations, functional disorders (trigeminal neuralgia, movement disorder, epilepsy, and pain), and malignant brain tumors.

On the other hand, radiation oncologists were unfamiliar with SRS such as high-dose irradiation. They did not believe in the effectiveness of high-dose irradiation of the body from a radiobiological perspective, and were even concerned that radiation side effects would increase. These physicians had been treating with fractionated radiotherapy (RT) to reduce radiation side effects and planning target volume margins to minimize treatment uncertainty, as they were in an era of undeveloped imaging techniques. However, advances in radiotherapeutic and radioimaging technology have eliminated uncertainty in precision and high-dose radiation therapy. Subsequently, stereotactic body radiotherapy (SBRT) was derived from SRS with improvements in radiation technology, using a small number of fractions with a high degree of precision within the body, unlike traditional fractionated RT [3].

The terms “SRS” and “SBRT” were used for central nervous system (CNS) and non-CNS anatomic sites, respectively, and in both cases involve the delivery of a

high biologically effective dose in 1–5 fractions to small, focal, well-defined targets while minimizing nontargeting dose. Some physicians favor alternative nomenclature such as “SABR” (“stereotactic ablative radiotherapy” or “stereotactic ablative brain radiation” or “stereotactic ablation body radiotherapy”).

Linear accelerator (LINAC)-based systems for SBRT are more readily available, and due to the low fractionation dose, larger tumors can be treated. The radiobiological rationale for dividing the prescribed total dose into 25–30 fractions is mainly to increase the likelihood of targeting tumor cells at the most radiation-sensitive stage of the cell cycle [4]. In contrast, SRS relies on a single high radiation dose, potentially affecting tumor cells in the non-dividing phase. The physical properties of SRS allow steep radiation gradients in the tumor margins, which are important for maintaining a low dose for adjacent structures. Although it is known that some tumors that resist fractionated RT may respond to SRS, differences in the exact radiobiological properties of the two modalities are still an issue of debate to some extent [5]. Along with the evolution of hypofractionated regimes a continuum has also emerged between RT and SRS, and sometimes the distinction might be unclear. The most widely accepted definition of what constitutes radiosurgery seems to be that of the Association of Neurological Surgeons and the Congress of Neurological Surgeons in 1996, which defines radiosurgery as a maximum of five treatment sessions (however, it is typically performed in a single session) [6]. The aim of this review is to discuss the distinction between RT and SRS based on radiobiology and radiophysics as well as several radiotherapeutic instruments.

STEREOTACTIC RADIOSURGERY

Although Leksell first introduced the concept of radiosurgery, SRS became more popular in the late 1980s through technological advances. SRS delivers radiation at a very high intensity, all at once, to a small area. It is a way of treating brain disorders with a precise delivery of a single high dose of radiation in a one-day session. The benefits of SRS are that it is a non-invasive treatment for patients who are not candidates for open neurosurgery (due to age, medical condition, or personal preference) that use irradiation and computer targeting to direct focused radiation to specific targets in the brain, thus minimizing injury to surrounding structures.

SBRT developed approximately a decade after SRS in 1994. Swedish physicist Lax and radiation oncologist Blomgren, both of the Karolinska Hospital in Stockholm, demonstrated that similar local control outcomes could be achieved at nonbrain body sites

with one or a few fractions, even if the targeting and immobilization issues for nonbrain sites were more complicated [7,8].

Although the original concept of SRS is treated as single-session irradiation, fractionated SRS has recently been considered for relatively large volume lesions. However, the therapeutic basis for fractionated SRS based on traditional radiobiology has yet to be explained. Nevertheless, many clinical studies have demonstrated the safety and efficacy of fractionated SRS as well as the fact that it potentially reduce SRS-related complications [9–12]. More research is needed on the optimal radiation dose and frequency for each disease.

STEREOTACTIC RADIOTHERAPY

During the 1920s to 1940s, French radiation oncologists Coutard [13] and Francois Baclesse treated with various fractionations of RT lasting from 2 weeks to 10 months for patients with laryngeal and breast cancers. They demonstrated that the uncomplicated control rate peaked at 6 to 8 weeks.

Stereotactic RT delivers radiation at different times, at lower intensities, and to larger areas. One benefit of this technology is its ability to easily treat very large tumor volumes by treating overtime during cell division. Conventional fractionated RT has been developed on the basis of radiobiology, that is, the 4Rs. The 4Rs represent repair, repopulation, redistribution, and reoxygenation of cells, and have recently been expressed as the 5Rs, including radiosensitivity. “Repair” means that an initially damaged cell regains or keeps its ability to contribute to organ function for a normal organ. “Repopulation” is when cancer cells and cells of acutely reacting normal tissues proliferate during the course of therapy. “Redistribution” refers to differential cell-killing effects in which radiation sensitivity varies depending on the cell cycle. “Reoxygenation” is a phenomenon characterized by the reduction of oxygen use and the reoxidation of hypoxic cells and the sensitivity to more radiation, as radiation kills more sensitive toxic cells. In summary, “repair” and “repopulation” contribute to radiation protection or radioreistance, and “redistribution” and “reoxygenation” contribute to radiosensitivity.

Unlike conventional RT, hypofractionated RT has been devised to reduce the number of fractions by increasing fractionated doses. This had caused confusion as regions overlapped with fractionated SRS, and the distinction between SRS and RT became more ambiguous in the mixture era. SRS and RT are compared in Table 1. With these changes over times, the investigation of the optimal dose and fraction number is becoming a more important area of study.

Table 1. Comparison of radiosurgery and radiotherapy

Variable	Radiosurgery	Radiotherapy
Dose per fraction	6–30 Gy	1–2 Gy
Fraction number	1–5 fractions	10–40 fractions
Irradiation time	30 min–several hr	Within 10 min
Purpose	Tumor ablation	Tumor control
Target	Gross tumor volume only	Gross tumor volume and microscopic extension
Dose distribution	Heterogeneous	Homogeneous
Dose gradient	Steep slope	Shallow slope
Prescription isodose line	< 50–95%	< 90–95%
Planning target volume margin	< mm	< cm
Biological effect	Vascular damage Immunological reaction	Repair Reoxygenation Repopulation Reproduction

Table 2. Advantages and disadvantages of stereotactic radiosurgery (SRS) from a radiobiologic perspective: the five “R’s”

Parameter	SRS advantage	SRS disadvantage
Repair	Improved tumor targeting enables dose reduction and fraction saving for normal tissues	Repair cell cycle that separates tumor response from damage inhibition and normal tissue toxicity
Reoxygenation	None	Increased radioresistance by reducing inter-fraction reoxygenation
Repopulation	Elimination of tumor repopulation during shorter treatment (especially relevant for radioresistant tumor stem cells)	None
Redistribution	None	Higher probability of catching cells in their vulnerable cell cycle states by more fractionated radiotherapy
Radiosensitivity	Reduced variability in tumor radiosensitivity (endothelial cell apoptosis through vascular damage by a single-tumor dose of more than 10 Gy)	None

RADIOBIOLOGY FOR STEREOTACTIC RADIOSURGERY

Historically, conventional fractionated RT has been interpreted biologically with the parameters, repair, reoxygenation, redistribution, repopulation, and (less commonly) radiosensitivity. From this traditional radiobiologic perspective, the pros and cons of SRS are summarized in Table 2.

Additionally, biological evidence of SRS is suggested to indicate immunologic effects and vascular damage. High-dose irradiation may have immunologic effects that differ substantially from conventional fractionation [14]. Furthermore, SRS is believed to contribute to cancer cell destruction by causing circulatory failure and apoptosis by vascular damage [15]. This biological basis provides therapeutic evidence for SRS, which has not been explained by traditional radiobiology.

Repair

It is widely assumed that irradiated normal tissue can respond better to repetitive cycles of DNA damage than can tumors with respect to intrinsic abnormalities in damage repair systems [16]. Thus, many irradiation fractions progressively separate normal tissue toxicity seen in tumors. While the magnitude of this differential response is limited by decreasing the fraction number in SRS, it is offset by a reduction in normal tissue damage associated with precision dose delivery.

Reoxygenation

Tumors commonly exhibit a hypoxic status, increasing radiation resistance due to the lack of fixation of free radical damage [17]. While conventional fractionated RT facilitates reoxygenation by reducing the overall oxygen demand, SRS theoretically reduces the effect of reoxygenation properties. However, it has been demonstrated that high-dose irradiation (> 10 Gy) activates a rapid endo-

thelial apoptotic response, resulting in changes in tumor perfusion and hypoxia [18,19]. This raises the possibility that high-dose irradiation could affect the response to subsequent fractions via changes in tumor oxygen status.

Repopulation

Withers [20] reported that after approximately 3 weeks of RT, repopulation of tumors was observed that would require additional RT. After that, conventional fractionated RT was continuously delivered to prevent prolongation of treatment. For SRS, rapid delivery of the tumoricidal dose provides significant benefits, especially for rapidly dividing tumor cells, to inhibit all tumor expansion.

Redistribution

Both conventional and hypofractionated RT will selectively kill cells in the most sensitive part of the cell cycle, G2/M. To date, the existence of subpopulations of tumor cells circulating at different rates and the complexity of proactively measuring the ideal time for subsequent investigations have not proven to be impossible challenges to exploiting this synchronization. However, reducing the fraction number alters the probability of irradiation when entering the radiosensitive phase.

Radiosensitivity

SRS mitigates differences in tumor killing that are directly attributable to variations in individual tumor cell radiation sensitivity. Increasing the fraction size and decreasing the fraction number may provide fewer opportunities for the selection and outgrowth

of resistant stem cells. These results are suggested to be due to vascular damage following the aforementioned irradiation dose of more than 10 Gy [18,19].

RADIOTHERAPEUTIC MACHINES

The characteristics of each radiotherapeutic machine are described in Table 3.

Linear accelerator

CyberKnife

The most differential feature of CyberKnife is that it is a light-weight LINAC RT device equipped with a robotic arm with 6° of freedom of movement. The advantage of this device is that it does not require fixation with a rigid frame and can treat with submillimeter accuracy. CyberKnife has five tumor-tracking systems: six-dimensional skull, fiducial markers, X sight spine, X sight lung with synchrony, and fiducial with synchrony. Through these features, the CyberKnife provides maximum flexibility in treating lesions in all parts of the body noninvasively. However, the CyberKnife has the disadvantage that the treatment time is extended because verification is repeated before each beam is delivered. Additionally, large volumes are not suitable because “dose painting” from one edge of the tumor to the other is the principle by which it works. Therefore, general indications of CyberKnife are recurrent and residual tumors after prior RT as well as small tumors in the lung, liver, and spine, which can be effectively treated.

Table 3. Radiotherapeutic instruments

Type	Instrument	Source	Energy range	Characteristic	Year	Company	Country
Accelerator unit	Linear accelerator						
	CyberKnife	Photon	6 MV	Robot-arm gantry	2007	Accuray	USA
	TomoTherapy	Photon	6 MV	Helical beam	2007	Accuray	USA
	Novalis Tx	Electron	6, 9, 12, 15, 18 MeV	Micro-MLC	2009	Varian	USA
	Versa HD	Photon	6, 18 MV				
		Electron	8, 12, 15, 18 MeV	FFF beam	2009	Elekta	USA
	TrueBeam	Photon	4, 6, 10 MV	High dose rate			
		Electron	6, 9, 12, 16, 20 MeV	FFF beam	2012	Varian	USA
	MRIdian	Photon	6, 10, 15 MV	High dose rate			
		Photon	6 MV	FFF beam	2019	ViewRay	USA
Radionuclide unit	MR-guide (0.35T)						
	Proton accelerator	Proton	70–250 MeV	Bragg peak	1954	LBNL	USA
	Carbon accelerator	Carbon	55.6–430 MeV	Bragg peak	1994	NIRS	Japan
				High BED & LET			
Radionuclide unit	Gamma Knife	Cobalt	0.25–3.5 MeV	Emitted radiation	1968	L. Leksell	Sweden

MLC: multi-leaf collimator, FFF: free flattening filter, MR: magnetic resonance, BED: biologically equivalent dose, LET: linear energy transfer, LBNL: Lawrence Berkeley National Laboratory, NIRS: National Institute of Radiological Sciences.

TomoTherapy

The biggest feature of TomoTherapy is its helical beam delivery, followed by a dedicated intensity-modulated RT system (IMRT). The radiation characteristics of this machine are the narrow fan beam delivery, lack of flattening filter, and increased shielding of the collimators. Briefly, the beam delivery method of TomoTherapy is similar to that of computed tomography. One of the major advantages of TomoTherapy lies in avoiding field junctions and dose gradients, especially for complex and long target volumes. Furthermore, by using helical treatment techniques, optimal savings of normal tissues can be reached while the target volume is homogeneously covered with irradiation dose. These machinal features allow TomoTherapy to be used as an IMRT-specific machine.

Novalis Tx

Novalis Tx is a kind of LINAC that is equipped with 2.5 mm micro multileaf collimators, a robotic couch, an optical tracking system, and X-ray-based image verification to provide high accuracy radiation delivery. It consists of 120 leaves, which includes 64 with 2.5 mm inner leaves and 56 with 5 mm outer leaves. These structural features make Novalis Tx more suitable for SRS by creating sharper penumbra and steep gradients between the target and normal tissue, unlike other conventional LINAC machines.

Versa HD and TrueBeam

Both Versa HD by Elekta and TrueBeam by Varian are LINACs with high-dose-rate flattening filter-free photon modes and electron modes. Based on conventional radiobiology, high-dose-rate irradiation was thought to affect late responding normal tissues, which was feared to increase the risk of late RT complications. However, high-dose-rate RT was introduced to reduce the treatment time as the RT accuracy and precision improved. For this, a flattening filter, which leads to homogeneity within the target, was removed, and a fast-paced multileaf collimator was developed. Despite various concerns at early installation, these machines are now widely available due to their efficiency and accuracy in treatment.

MRIdian

MRIdian is a LINAC that can be used to treat under magnetic resonance imaging (MRI) guidance. The early version of the MRIdian used three cobalt-60 sources beginning in 2014, while the first patients were treated with the LINAC version in 2017. MRI-guided RT allows daily MRI delineation of superior soft-tissue contrast for the patient setup and an on-table adaption of the treatment plans. An automated beam gating system is enabled by MRI and structural tracking. The greatest strength of this machine is that it can reflect the volume of tumors that change during RT and minimize setup

errors of patients in real-time through MRI guidance.

Proton accelerator

In 1946, Wilson [21] first suggested that proton beams could be used for cancer patients. He described how proton beams accumulate energy as they enter the body on their way to tumors. A smaller amount of energy is released first and a much larger amount of beam energy is released at the end of the path, called the “Bragg peak”. The first therapeutic application of proton beams proposed by Wilson started the Berkeley Radiation Laboratory, USA, in 1954 [22]. These radiophysical features provide less radiation to normal tissues resulting in fewer RT complications, especially secondary malignancy. Although it has not yet shown better clinical outcomes than other LINAC machines, it is considered that proton accelerators might be effective in childhood cancer patients. These are currently being used to treat patients at the National Cancer Center and Samsung Medical Center in Korea.

Carbon accelerator

In 1994, carbon ion radiotherapy (CIRT) was initiated at the National Institute of Radiological Science (NIRS) in Japan using the world's first heavy ion accelerator complex (Heavy Ion Medical Accelerator in Chiba, HIMAC) [23]. The NIRS adopted carbon ions among several types of ion species because of the high linear energy transfer (LET), which enables sufficient dose delivery within the target volume, particularly at the Bragg peak. Furthermore, carbon ions show high relative biological effectiveness (RBE) compared to conventional low-LET radiation in cell killing. Through these characteristics, CIRT has favorable dose distribution compared to photon and proton beams, providing a higher tumor control probability while minimizing the dose for the surrounding normal tissues. There are currently 13 centers treating with CIRT for almost every type of malignancy. By 2017, more than 20,000 patients had been treated with CIRT, mainly enrolled in phase I–II clinical trials that hold promise for safety and efficacy data [24,25]. Construction for CIRT is currently underway at Yonsei University Severance Hospital in Korea.

Gamma knife

In the 1950s, Leksell and Larsson tried to create a radiotherapeutic machine that combined a proton beam with a stereotactic device in the brain, eventually, in 1967, they developed the first GK prototype that used a cobalt-60 source. Cobalt-60 decays through beta decay to a stable isotope of nickel with a half-life of 5.26 years. During decay process, one electron with an energy of up to 315 keV and two gamma rays with energies of 1.17 MeV and 1.33 MeV are emitted. It is called a GK because of its application of such emitted

Table 4. Clinical responses to stereotactic radiosurgery

Indication	Dose	Efficacy	Complication
Metastatic brain tumor [30,38]	16–30 Gy	81–98% local control rate	0.4
Metastatic spine tumor [26,35]	16–30 Gy	85–90% local control rate 54% complete pain response	Vertebral compression (9.4%) Neurological injury (0.2%)
Benign brain tumor [28,34]	12–16 Gy	91–100%	5–7%
Arteriovenous malformation [27,31]	18–25 Gy (median 20 Gy)	Obliteration rate: 19–88% (median 38%)	9.1% in thalamus 12.1% in the brainstem 1.4% in other locations
Cavernous malformation [29,37]	10–25 Gy	Hemorrhage risk: 23.6% → 3.2% (beyond 2 yr) 78% seizure control rate	Morbidity (2.4–6.7%) Mortality (0–2.3%)
Trigeminal neuralgia [36]	50–90 Gy	17.3–100% (mean 53%)	Hypesthesia (0–68.8%)
Essential tremor/parkinsonian tremor [32]	130–150 Gy	54.2–100% (mean 88%)	Transient hemiparesis (2%)
Epilepsy [33]	20–24 Gy	28.5–67.0%	1–4%
Obsessive compulsive disorder [39]	120–180 Gy	45.0–71.4%	Mood disturbance (7.8%)

Benign brain tumors include meningioma, vestibular schwannoma, pituitary adenoma, etc.

gamma rays to clinical effects. Inside the GK unit, there are approximately 200 sources (201 sources in model U, B, and C, and 192 sources in Perfexion and Icon) aligned with the collimation system, which can be focused on a very precise accumulation to fill the beam. Additionally, the Leksell frame used by the GK defines a reference coordinate system that can provide points in the brain with high precision. Based on these characteristics of the GK, it does not require quality assurance of radiation energy for each patient, unlike other accelerator instruments. Additionally, due to the radiation properties of GK devices, a labyrinth structure for shielding radiation is not required, and multiple high-dose irradiations do not burden the treatment machine. These features are different from other accelerator-based radiation machines.

INDICATIONS OF RADIOSURGERY

Leksell used the GK prototype for 12 years from 1967 to treat patients with brain tumors as well as functional neurosurgery, i.e., pain, movement disorders, and even specific behavioral disorders that did not respond to conventional psychiatric treatments. Since that time, the patient indications for treatment have not changed much. Currently, SRS is adopted primarily to treat benign brain tumors, arteriovenous malformations, acoustic neuromas, brain metastases, and other brain tumors, as well as trigeminal neuralgia (Table 4) [26–39].

In particular, the use of SRS without whole-brain RT (WBRT) has increasingly been used to avoid WBRT-related toxicity for patients with a limited number of brain metastases [40]. Based on several studies, the omission of WBRT in patients with ≤ 3 brain metastases has been widely adopted [41,42]. Currently, SRS treat-

ment for > 3 brain metastases has been adopted by the National Comprehensive Cancer Network guidelines [43].

CONCLUSION

Through the advancement of radiotherapeutic technology, the boundaries between RT and radiosurgery are blurring. This mixture era creates confusion for many doctors, especially novice neurosurgeons. Deeper radiotherapeutic knowledge will certainly be of help to neurosurgeons dealing with radiation therapy. Therefore, this review provides radiotherapeutic information for neurosurgeons to familiarize them with radiation therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

I would like to express my deep gratitude to Cheol Wan Park, a senior neurosurgeon and who offered me the way to radiation oncologist. It is undoubtedly all thanks to him that I was able to write this review as a double board, neurosurgery and radiation oncology.

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