



Stereotactic Radiosurgery

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Stereotactic radiosurgery is one of the most sophisticated forms of modern advanced radiation therapy. Unlike conventional fractionated radiotherapy, stereotactic radiosurgery uses a high dose of radiation with steep gradient precisely delivered to target lesions. Lars Leksell presented the principle of radiosurgery in 1951. Gamma Knife® (GK) is the first radiosurgery device used in clinics, and the first patient was treated in the winter of 1967. The first GK unit had 179 cobalt 60 sources distributed on a hemispherical surface. A patient could move only in a single direction. Treatment planning was performed manually and took more than a day. The latest model, Gamma Knife® Icon™, shares the same principle but has many new dazzling characteristics. In this article, first, a brief history of radiosurgery was described. Then, the physical properties of modern radiosurgery machines and physicists' endeavors to assure the quality of radiosurgery were described. Intrinsic characteristics of modern radiosurgery devices such as small fields, steep dose distribution producing sharp penumbra, and multi-directionality of the beam were reviewed together with the techniques to assess the accuracy of these devices. The reference conditions and principles of GK dosimetry given in the most recent international standard protocol, International Atomic Energy Agency TRS 483, were shortly reviewed, and several points needing careful revisions were highlighted. Understanding the principles and physics of radiosurgery will be helpful for modern medical physicists.

Keywords: Gamma Knife, Radiosurgery, Dosimetry, Standard protocol

Introduction

Stereotactic radiosurgery (SRS), which has been used for more than 60 years, is a form of external beam radiation therapy. Soon after Wilhelm Röntgen discovered the X-ray in 1895, people used it to treat cancers such as basal cell carcinomas. Because the energy was not high enough then, X-rays could cure only cancers on the surface of the body in the beginning. In 1946, Wilson [1] suggested using protons to treat deep-seated tumors using the intrinsic characteristic of charged particles much more massive than electrons, the Bragg peak. Before John Lorence and Cornelius Tobias

began applying deuteron or helium beams to sella turcica tumors at Berkeley in the USA [2], Leksell [3] in Sweden presented the concept of SRS in 1951. He defined radiosurgery as “delivery of a single, high dose of radiation to a small and critically located intracranial volume.” Because his goal of radiosurgery at that time was to make a destructive lesion in a healthy brain to treat functional neurological diseases, he proposed using a “single, high dose radiation.” Single-session irradiation was the critical property of SRS. It did not take the radiobiological advantages of fractionation. It required high accuracy in positioning and steep dose distribution. In 1953, he treated two patients with trigeminal

neuralgia using an X-ray tube mounted on a stereotactic ring [4]. Although he was able to get desirable results, still no machine was available thoroughly satisfying his requirements; a new device was needed. To develop a machine realizing his idea, he cooperated with medical physicists, Kurt Lidén and Börje Larsson. In 1967, they treated a young patient with craniopharyngioma using a novel machine, Gamma Knife [5], which consisted of 179 cobalt 60 (^{60}Co) sources placed on a hemispherical steel helmet. Being inspired by successful results of SRS using Gamma Knife (Elekta Instruments AB, Stockholm, Sweden), individuals devised specific tools for SRS using clinical linear accelerators (linac) in the 1980s. Nowadays, many machines are using linacs for SRS, such as Novalis (Brainlab AG, Feldkirchen, Germany), CyberKnife (Accuray, Sunnyvale, CA, USA), and TomoTherapy (Accuray, Sunnyvale, CA, USA).

Principle and Technique

1. Principle of stereotactic radiosurgery

The most prominent feature of SRS compared with typical external beam radiation therapy is that SRS irradiates a high dose of radiation in a single-session. Although hypofractionated radiation therapy is also considered a form of SRS recently, the mainstream is still a single-session treatment. It means that SRS accomplishes its clinical outcomes with different radiobiological principles. Instead of anticipating different responses of cells of various alpha-beta ratios, SRS expects every cell in a target to lose its ability to mitose. With an ideal SRS device, we can give a full lethal dose to a target and no irradiation to the surrounding normal cells. In reality, a dose distribution has a finite slope; therefore, some amount of radiation will go to the surrounding normal cells. When we try giving a high enough dose to irradiate malignant tumors, doses to the surrounding normal tissues usually rise over the tolerable limit. It characterizes the main indications of SRS mainly to benign tumors or vascular disease, whereas fractionated radiation therapy is more suitable for malignant tumors.

2. Technique for radiosurgery

Though SRS shares similar approaches with modern advanced radiation therapies, it still requires higher-level positioning accuracy, steeper dose gradient, and more careful dose verification. Three main factors determine the positioning accuracy. The mechanical accuracy of a device determines the accuracy to guide the radiation to a predefined target. Modern radiosurgery devices have verified mechanical accuracy of less than a millimeter. The accuracy of the images used for SRS is more problematic than the mechanical accuracy. Computed tomography (CT) images can be easily taken with submillimeter resolutions and thickness, and they are almost free from image distortion. However, magnetic resonance (MR) images usually have slices thicker than a millimeter for better signal-to-noise ratios. Moreover, they have image distortion errors coming from nonuniform magnetic fields. Image distortion errors are even more severe for 3T MR images. It has been proven that obtaining mean MR image distortion errors of approximately half a millimeter is possible using 1.5T MR machines [6]. 3T MR images must be carefully checked if their distortion is well confined to be suitable for SRS. The third factor related to the positioning accuracy is patient motion during irradiation. In cases of intracranial SRS, we can expect no movement of the patient's head when a stereotactic frame is fixed. For frameless intracranial and body SRS, the target always moves, voluntarily or involuntarily. New SRS devices are equipped with patient-monitoring systems so that the motion can be limited to a submillimeter range or intervene irradiation otherwise.

Getting dose distributions with a gradient as steep as possible is the core technique in SRS devices. As the machine makes the sharper declination of the absorbed dose, we can concentrate more radiation to the target lesion. It means that we can treat larger lesions and more malignant tumors using SRS. In addition, increasing the dose per fraction is crucial in fractionated radiation therapy since we can treat more patients using a machine during a given period. It is a major research topic in the particle therapy field to secure profitability. How to focus radiation to produce sharp dose distributions is the primary difference among radiosurgery machines. Gamma Knife arranged approximately 200 ra-

radioactive sources on a hemispherical or cylindrical surface so that the beams cross at the center. Novalis rotates a gantry along several arcs around a common center. CyberKnife can beam photons in any direction, but usually less than 150, and can generate dose distributions in not isocentric ways.

Verification of the absorbed dose is a fundamental prerequisite of SRS because patients can get more harm from the concentrated high dose radiation. Assessing relative dose distributions with high precision is more manageable than measuring the absolute value of the absorbed dose. Standard dosimetry using radiochromic films can assure the accuracy of relative dose distributions. Gamma index values higher than 97% were verified using 1 mm/3% criteria in various situations for the Gamma Knife planning system [7]. Accurate measurement of the absolute value of the absorbed dose to water for an SRS machine is a critical issue since smaller fields instead of standard radiation therapy fields are used. The International Atomic Energy Agency (IAEA) and American Association of Physicists in Medicine (AAPM) published an international code of practice, IAEA TRS 483, in 2017 [8]. TRS 483 recommended new protocols to determine the absolute value of the absorbed doses in machine-specific reference (MSR) fields and described the relative output factors for smaller fields to MSR fields. Though medical physicists in the SRS area can be relieved by TRS 483, some problems remain.

Machines for Stereotactic Radiosurgery

1. Machines with radioactive sources

Gamma Knife is the first radiosurgery-dedicated device

and the most widespread over the world though it can treat only intracranial lesions. The earliest model was built-in 1967. Several upgrade models were introduced, and the latest models are Gamma Knife Perfexion and Icon (Fig. 1a). The Icon model shares the same irradiation system with the Perfexion model. The additional components of the Icon model are a cone-beam CT (CBCT) and a high-definition motion management (HDMM) system, which are used for frameless SRS. Gamma Knife is the most straightforward device ever introduced in the radiosurgery field. Approximately 200 radioactive ^{60}Co sources are distributed around the center, where the radiation is more than 200 times stronger than a single source. At the time of installation, the radioactivity of each source is near 30 Ci, and the absorbed dose rate to water at the center of an 8-cm-radius solid water phantom is higher than 3.0 Gy/min. The iso-surface of the absorbed dose at the center is ellipsoidal because the sources are on a cylindrical surface. Since one ellipsoid—called a “shot” among Gamma Knife users—cannot conform to the target, multiple shots of various sizes are used to make a treatment plan. Bigger targets require bigger collimators. Gamma Knife SRS has been using an intensity-modulated irradiation technique from the beginning; a shot can cover more target volume when it is kept longer. The 192 sources of the Perfexion/Icon model are divided into eight sectors. Because each sector can be located on different-size collimators or blocked, the shape of a single shot can be deformed following the form of a target. By adjusting the location, size, shape, time, and angle of each shot, covering more than 98% of the target is readily possible as the irradiated portion of the surrounding normal tissue is less than 10% of the target volume.

Fractionated therapy using Gamma Knife was unpopular



Fig. 1. Modern stereotactic machines. (a) Gamma Knife, (b) Novalis Tx, and (c) CyberKnife.

because living with a stereotactic frame for several days is painful for patients. The mask-based SRS system of the Icon model provides a more appropriate method for performing fractionation using Gamma Knife. A frame in the frame-based SRS fulfills two roles—defining a stereotactic coordinate system and holding the patient's head during irradiation. In the mask-based frameless SRS using Gamma Knife Icon, the CBCT attached to the main body defines a fixed stereotactic coordinate system. The center of the CBCT images corresponds to a fixed point of the coordinate system. The patient's head is held with a plastic mask, but unacceptably large movements are still possible. The motion of the patient's head is monitored by the HDMM system based on an infrared camera, four fixed reflectors, and one reflector on the patient's nose. Limiting the motion under 1 or 1.5 millimeters is common.

Treatment planning is performed mostly using MR images because they are more suitable for target delineation. Co-registering the MR images to the reference CBCT images both before and after treatment planning is possible. If the treatment is fractionated, the patient setup is checked before every irradiation. The treatment plan is automatically corrected if deviations from the reference positions are detected. Studies with end-to-end tests of frameless Gamma Knife SRS showed submillimeter accuracy of the system, including the accuracy of the HDMM [9]. However, it should be emphasized that patient motion during irradiation should be thoroughly monitored and carefully controlled.

Several machines using ^{60}Co sources other than Gamma Knife can perform SRS. The Rotating Gamma System (RGS) uses 32 sources and obtains steep dose distributions by rotating the helmet containing the sources. While the old-type Gamma Knife used four heavy helmets to accommodate different-size collimators, the RGS put the collimators on a single helmet. Collimator size can be changed by rotating the helmet. This idea was transferred to the Icon model, which moves the sources back and forth to change the collimator size. Another system, ViewRay, succeeded in the concept of rotating radioactive sources and used three powerful ^{60}Co sources rotating 360° to generate a peek-like dose distribution at the center. In addition, ViewRay was equipped with a 0.3T MR imaging system, which enabled it

to perform real-time image-based SRS. Although it was the first MR-based radiotherapy machine, cobalt sources were replaced with a linac in later models.

2. Machines with a linear accelerator

When pioneers in linac SRS tried using conventional photon radiation therapy machines in the early 1980s, they were confronted with significant barriers. Dose rates were too low to finish treatment in a reasonable time. The absence of beam-shaping devices resulted in poor conformities. The insufficiently collimated beams with large penumbra failed to generate steep dose distributions. After various intensive studies, they could build linac-based SRS systems by attaching a specially devised equipment to the conventional linacs. Soon, these endeavors were carried over to the invention of linac-based SRS-dedicated machines. The Novalis system was the first leader [10]. Like conventional linac systems, Novalis rotates a gantry around an isocenter. However, it can change the shape of the S-band X-rays through the micro-multileaf collimators (MMLC) during rotation. It controls each leaf of the MMLC to deform the beam, mimicking the outline of the target in the beam's eye view. Various irradiation methods such as multiple coplanar arcs, fixed-shape conformal arcs, dynamically shaped conformal arcs, and intensity-modulated radiosurgery can be employed. The Novalis Tx radiosurgery platform is shown in Fig. 1b. It offers a dose rate of 1,000 MU per minute of photons in an energy range of 6 to 20 MeV. The average accuracy of the gantry rotation of a Novalis system is 0.3 mm, and that of the couch eccentricity is 0.6 mm [11,12]. Frameless SRS can be performed using the image-guided setup and the position verification systems. A CBCT system is integrated to check the patient's position before each treatment session. Target displacement is assessed by two independent built-in imaging systems requiring kilovoltage X-ray images during beam delivery or between the fields. The X-ray images are compared with the digitally reconstructed radiographic images. The patient's couch with 6° of freedom can correct the directional inaccuracy and rotational misalignments. The optical camera tracking system monitors the patient's movement during beam delivery. Target conformity is achieved by modulating the

gantry speed, the MMLC configuration, and the linac output. Modern linac-based radiation therapy systems adopted similar equipment using the same principle. Imaging systems such as the built-in CT and X-ray imaging system with digitally reconstructed radiographs are essential for image-guided radiation therapy. The optical tracking system and the couch with 6° of freedom are widespread and common in most advanced linac-based radiation therapy systems.

John Adler and coresearchers developed the CyberKnife in the early 1990s. It is a unique device in which a lightweight linac is mounted on a robotic arm, unlike other machines that rotate the linac (Fig. 1c). The linac moves around the target to predefined nodes. When it reaches a node, it fires the X-band gamma rays through narrow circular collimators or an MMLC. Even at a node, it can vary the irradiation angle and change the relative beam path by moving the patient. As a result, multiple thin pencil beams can cover the target and achieve desirable conformity. The newest version, the CyberKnife S7 system, can produce a dose rate of up to 1,000 MU per minute so that the overall treatment time can be decreased. The smallest width of the beam produced by its MMLC is 3.85 mm at an 800-mm source to acceptance distance. CyberKnife radiosurgery is a frameless procedure. The target is tracked using one of the three stationary tracking modes, that is, 6D skull tracking, fiducial tracking, or the Xsight spine-tracking systems. Two kilovoltage X-ray generators and amorphous silicon flat-panel digital detectors are used for target tracking. Images from the cameras are compared with digitally reconstructed radiographs initially and during the treatment, which are generated from CT images taken before the treatment. Motion tracking is possible using the Synchrony respiratory tracking system or the Xsight lung-tracking system. It is used along with an applicable target tracking system. Misalignments up to the predefined limits are corrected by realigning the robot manipulator. The more significant errors are corrected by adjusting the patient's couch [13]. In addition to SRS-dedicated machines, most of the up-to-date radiotherapy machines have options for SRS. Although SRS-dedicated machines are superior to them in some specifications, they use similar techniques and have an acceptable ability for SRS. Choosing a device for SRS seems to be a clinical issue rather than a technical issue.

Physics of Radiosurgery

1. General characteristics

While SRS takes a radiobiological approach different from that of conventional radiation therapy, related principles of physics are the same. The absolute value and relative distributions of the absorbed dose to organs must be measured as accurately as possible. In addition, studies on enhancing the dose concentration ratio, reducing the effect of organ motions, shortening treatment times, and many other subjects are mandatory. Still, the most fundamental object should be the safety of patients. Moreover, emphasizing that experimentally measured dose distributions should be comparison targets, not the calculated distributions on a computer screen, is also necessary. Many treatment planning systems display splendid dose distributions on a monitor, but it is the physicists' responsibility to verify its trueness.

Mechanical accuracies and relative dose distributions can be checked to submillimeter precision by regular dosimetry with radiochromic films. Two-dimensional analyses of irradiated films showed gamma index pass rates of larger than 95% under reasonable acceptance criteria. Testing dose distributions not only for some single shots but also for the real treatment plans composed of multiple complex fields is recommended.

2. Small-field dosimetry

The most severe radiophysical issue of SRS at this moment is how to measure the absolute value of the absorbed dose to water for small fields. Since small-field dosimetry is described minutely in another section, the discussion will be limited to some practical issues here. When a field size becomes smaller than a detector size, the dose measured at the active point of the detector is different from the actual value of the intended point because the measured value is an averaged value over the detector—volume averaging effect (VAE). Furthermore, lateral charged particle equilibrium (LCPE) is not satisfied—a lack of LCPE. One thing that needs to be clarified is that the characteristics of small fields (VAE and lack of LCPE) and resultant effects of be-

ing a small-field should be distinguished. Many articles, including TRS 483, described that the reduced dose rates of the small fields were due to the finite size of the primary source as one of the intrinsic characteristics. However, it is just a phenomenon occurring when the field size becomes smaller as a result of the overlapped penumbrae. The reduced dose rate is not one of the essential properties of small fields but one of the physical quantities that are difficult to measure accurately because the field became small. The lack of LCPE can be problematic since the relationship between the absorbed energy to a detector and the number of signals produced in the detector may be different from that determined under standard conditions. Since the output signal decreases as the absorbed energy is reduced due to the lack of LCPE, we can suppose that its effect is not significant. Furthermore, we can expect that it will be even smaller if we use solid detectors instead of an ion chamber. Since most of the secondary electrons are generated inside a solid detector, unlike an ion chamber, the effect of the lack of LCPE becomes smaller. The most fundamental problem is the VAE. We can avoid much deterioration related to the chamber walls, central electrode, and other materials of an ion chamber by using different types of detectors, such as diamond or scintillation detectors. However, removing the VAE is impossible as long as we try to measure the absorbed dose at a point with any type of non-zero volume detector.

In TRS 483, IAEA and AAPM advised using ion chambers as detectors to measure the absolute dose in reference fields of SRS devices. They defined a MSR field for each

type of SRS device. The MSR conditions for reference dosimetry of linac-based SRS machines given in IAEA seem to be reasonable. However, the MSR conditions presented for Gamma Knife have several inconsistent or inadequate expressions (Table 1). It recommended 16-cm-diameter phantom but specified 7 cm for the measurement depth for a PMMA phantom in the notes. Fix the phantom size to 8 cm or recommending a reference measurement depth of 8 cm in water is more appropriate. The unique definition of the correction factor for Gamma Knife confuses the readers more. Unlike those for other machines, the correction factors for Gamma Knife given in TRS 483 include the phantom correction factor though the same expression, $k_{Q_{MSR}, Q_0}^{f_{MSR}, f_{ref}}$, is used for all machines. The position of the ion chamber active point is decided in TRS 483, but not the orientation. Different orientation of the detector needs modification of the correction factors [14,15].

A single value of 32 cm is given as the source to surface distance. It may be correct for models B and C of Gamma Knife but not for the recent models, Perfexion or Icon. Because the sources are distributed on a cylindrical surface, defining a single value to the surface of a hemispherical phantom is impossible. Furthermore, 192 sources are divided into five rings; therefore, the distances from the source to the radiation focus are all different for the rings. The field was described as a circular one with a 16- or 18-mm diameter. The actual field shape is an ellipsoid, three-dimensional object. For the Perfexion or Icon model, the full width at half the maximum is approximately 22 mm along the x-

Table 1. Reference conditions for the determination of absorbed dose to water on Gamma Knife machines presented in TRS 483 [8]

| Influence quantity | Reference value or reference characteristics |
|--|---|
| Phantom material | Water or plastic (polystyrene, ABS, Solid Water, etc.)* |
| Phantom shape and size | Hemispherical atop a cylinder, 16-cm-diameter |
| Chamber type | Microchamber, cylindrical |
| Measurement depth z_{ref} | Center of the hemisphere [†] |
| Reference point of chamber | On the central axis at the center of the cavity volume |
| Position of reference point of chamber | At the center of the hemisphere |
| Source to surface distance | 32 cm |
| Field size | Circular, maximum available (1.6 or 1.8 cm diameter) [‡] |

*Different designs have been reported, but the more common type advised in a Gamma Knife systems is the hemisphere atop a water-filled or compact polystyrene cylinder.

[†]In polystyrene phantoms, the depth is usually 8 cm; for PMMA, it is 7 cm.

[‡]For Gamma Knife machines, the maximum field size available depends on the model: 1.8 cm diameter for the standard model (Gamma Knife 4 or 4C) and 1.6 cm diameter for the Perfexion model. For Rotating Gamma System (RGS) machines, the maximum field size available is 1.8 cm diameter. The machine-specific reference field is the field generated with all sources out.

direction (left to right of a patient) and the y-direction (back to the front of a patient) of the Gamma Knife coordinate system. It is slightly larger than 17 mm in the z-direction (head to feet). The 16 or 18 mm is just a “name” of the largest field collimator, not the actual field size.

TRS 483 defined a correction factor that is multiplied to the measured charge in addition to the standard N_{DW} value of IAEA TRS 398 for some commercial ion chambers [8,16]. They called this factor a “beam quality factor,” which is somewhat a misleading name. The beam quality correction factor defined in TRS 398 is a factor to consider different beam qualities between a standard laboratory and a clinical site. In contrary, the beam quality correction factor in TRS 483 includes additional factors related to the field shape and size, detector characteristics, and sometimes the phantom factors, not only the beam quality. Calling this an “MSR correction factor” rather than a beam quality correction factor seems to be more appropriate. The MSR correction factors for Gamma Knife provided in TRS 483 are from thorough Monte Carlo simulations. However, those values have not been published in peer-reviewed journals yet. In this data, the detector orientation has not been mentioned. According to Mirzakhani et al. [15], the detector orientation is different for the solid water phantom and the ABS phantom. Updating these values by including the results of more recent published studies is mandatory [14-18]. Once the absolute value of the absorbed dose rate is correctly measured for an MSR field, the field output factors should be determined. The procedure and measured or calculated values of the field output factors were well described in TRS 483.

Future of Radiosurgery

Once there was a clear distinction between SRS and radiation therapy, single versus fractionated therapy, SRS could be regarded as more advanced in conformity using MMLC and multiple beams. Nowadays, telling which is SRS and which is radiotherapy is more difficult. An increasing number of clinicians are using hypofractionation for their SRS patients. The state of the art technology of new radiotherapy devices can generate treatment fields comparable to those of SRS. However, it is evident that steeper dose dis-

tribution and accurate positioning are beneficial even for fractionated therapies. If we can build a marvelous machine that can provide a stepwise dose distribution, every lesion will be treated in single-session irradiation. Increasing the dose slope is one of the ultimate goals of medical physicists. As technologies advance more, discrimination between the SRS and radiotherapy will recede. However, the significance of the duty of medical physicists, verifying highly concentrated doses and securing patients’ safety, will be much more critical.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

Author Contributions

Conceptualization: Hyun-Tai Chung and Dong-Joon Lee. Investigation: Hyun-Tai Chung and Dong-Joon Lee. Resources: Hyun-Tai Chung and Dong-Joon Lee. Supervision: Hyun-Tai Chung and Dong-Joon Lee. Writing—original draft: Hyun-Tai Chung. Writing—review & editing: Dong-Joon Lee.

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