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Radiosurgery Techniques for Brain Metastases

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ET, BP and US designed the study, wrote the protocol and the first draft of the manuscript. Authors AK, SS, DS and NKD managed the analyses of the study. Authors EYA and YB managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

As a notable cause of cancer-related morbidity and mortality, brain metastases (BMs) represent the most prevalent intracranial tumors arising in up to 40% of all adult solid tumors during the course of treatment. Intracranial stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) gained wide appreciation by the radiation oncology communities for the treatment of BM with regards to the grim prognosis of such patients after alternative therapies, including the whole brain radiotherapy (WBRT). Additional concerns on the neurocognitive deterioration and comparably low tumor control rates offered by the conventional WBRT further quickened the implementation of SRS to the daily practice of radiation oncology clinics. However, the striking diversities among the treatment algorithms and the treatment planning systems of the gamma knife-, linear accelerator- (LINAC), tomotherapy-, robotic Cyberknife-, or the proton therapy-based SRS render the administration of SRS/FSRT challenging. Acknowledging these difficulties, the present review intended to offer a thorough outline of the main principals of the SRS/FSRT technique from the initial patient fixation to the final machine and dose delivery quality assurance treads.

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1. INTRODUCTION

As a significant cause of cancer-related morbidity and mortality, brain metastases (BMs) represent the most frequent intracranial tumors emerging in up to 40% of all adults with solid cancers, which is relatively 3 to 20 times more prevalent than the primary brain tumors [1-3]. Even though many cancers can metastasize to the brain, yet lung and breast cancers and malignant melanomas account for most BM cases [1-4]. Diverging from the progressive gains in the diagnostic tools and treatment modalities, diagnosis of BM is almost invariably linked to a bleak prognosis with only median 6 months survival even after the ordinarily practiced whole-brain radiotherapy (WBRT) [3,4]. This bleak prognosis is to a large extent connected with the impermeability of the blood-brain barrier to many chemotherapeutic and targeted agents, rendering the brain a sanctuary site for numerous solid tumors [4].

Subsequent to its initial announcement by the eminent neurosurgeon Lars Leksell in the 1950s, the intracranial stereotactic radiosurgery (SRS) attained wide gratitude by the radiation oncology community for the treatment of BM with regards to the dismal prognosis of such patients after systemic chemotherapy, neurosurgical tumor resection, conventional WBRT, and as lately the targeted therapies [4]. Further worries about the neurocognitive decline and comparably low tumor control rates afforded by the conventional WBRT further accelerated the successful implementation of SRS to the routine practice of radiation oncology clinics in either form of the gamma knife, linear accelerator (LINAC), tomotherapy, robotic Cyber knife, the proton therapy-based SRS [5]. Intracranial SRS can be delivered through single-fraction SRS or fractionated stereotactic radiotherapy (FSRT) regimes (customarily ≤ 5 fractions) in the definitive or postoperative settings, and lately preoperatively [6].

Overall the SRS or FSRT planning and delivery are challenging tasks due to the accessibility of various treatment machines with diverse planning and treatment algorithms and the variability of the intention and the timing of the SRS relative to the other treatment options, like the neurosurgical or systemic therapies. Acknowledging these difficulties, the present review intended to offer a thorough outline of the main principals of the SRS/FSRT technique from the initial patient fixation to the final machine and dose delivery quality assurance steps.

2. SRS TECHNIQUES

SRS represents any method of the execution of ionizing radiation to any part of the body with a definitive goal of destruction of a target volume completely without significant toxicities to neighboring healthy tissues [7]. Ionizing radiation can be refined either from the radioisotope sources like Cobalt-60 in Gammaknife, X-ray-generating machines in linear accelerators (LINAC), or positively charged protons from the cyclotrons and synchrotrons [5]. A typical modern GK unit incorporates 192 or 201 radioisotopes of Cobalt-60 in a hemispherical array that converges and focuses on the target volume at a source to target distance of 40 cm. Separate beamlines got from each source prove no clinical significance, but countless beamlines are simultaneously focused on the intended objective volume to achieve the prescribed dose with the resultant benefit of the desired sparing of the neighboring healthy tissues [8]. In LINAC-based SRS, computer-assisted multi-leaf collimators are utilized to shape the radiation beam by various LINAC systems those are fit for the execution of the SRS by conveying dynamically shaped isocentric arc beams via intensity-modulated radiotherapy (IMRT) technique. The robotic armed Cyber Knife is a modern 6-MV LINAC variant that uses non-isocentric cone beams. Despite the inherent technical differences, proton generating treatment machines utilize the equivalent radiosurgical principles alike the LINACS. Of note, though various systems are commercially available for SRS applications with individual pros and cons, they all utilize the same fundamentals. These are;

- Immomibization and setup
- Stereotactic brain imaging
- Image quality assurance
- Definition of the target and critical organ volumes
- Treatment planning
- Plan quality assurance
- Periodic quality assurance of the devices

2.1 Immobilization and Setup Procedures

Following the diagnosis of BM, the initial step of any SRS application is the best possible

immobilization of the likely patient for the forthcoming imaging and planning procedures, which will without a doubt determine the accuracy of the treatment plan and conveyance of the prescribed doses to the intended target volumes (TV). Moreover, because the chief goal of SRS is to restrict the high-dose to the TV in a highly conformal fashion with simultaneous avoidance of surrounding healthy tissues by the creation of steep-dose gradients around the TV, this step is of central significance for the plan quality and the accomplishment of the best tumor control rates [9-11]. Suitable immobilization devices either in the form of fixed type invasive frames or non-invasive masks can be used for the maximum restriction of the intra- and interfraction patient movements [10] (Fig. 1). Inter- and intrafraction motions represent the two major sources of errors restricting the capacity of the administrator in the accomplishment of the best plan and dose delivery quality for the mask-based immobilization. In this respect, image guidance was noted to represent the most convenient strategy to reduce the interfraction motion errors from 3.9 to 0.9 mm with just a residual intrafractional motion-related deviation of 0.9 mm [11,12]. Thusly, considering the unforeseeable hazard for 1.6 to 3.9 mm intrafraction errors, image guidance must be compulsorily used for frameless SRS to convey the arranged treatment plan with the highest precision rates, while frame-based techniques ought to consistently be favored where image guidance is not accessible.

2.2 Imaging and Image Quality Assurance

The ensuing crucial step of SRS is imaging and its quality assurance which remains the key for each resting pace of a precise SRS planning and treatment conveyance. For this goal, thin-sliced (≤ 2 mm) MRI is brilliant for the demonstration of the tumor and remaining intracranial structures. The fusion of MRI with CT scans may be of use for the discernment of the bone invasion and reduction of the dose non-uniformities. Other imaging modalities like positron emission tomography with fitting tracers, functional MRI, and angiography may sustain profitably, if convenient. However, the quality of scans obtained from each imaging method and the resultant co-registered images ought to be assured by an experienced team in charge, to be specific the radiation oncologist, radiation physicist, radiologist, and the nuclear medicine physician.

2.3 Contouring the Target Volume

Contouring of the gross tumor volume (GTV) and organs at risk (OARs) is typically performed with the utilization of the co-registered axial CT and MRI images (Fig. 2). Ideally, to enhance the accuracy of the volumetric delineation, the contouring process ought to incorporate each of the axial, sagittal, and coronal axis sequences of T1-weighted and T2-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI with slice thicknesses ≤ 2 mm. CT and MRI fusion precision should be checked thoroughly before the contouring process. Only the visible contrast-enhanced tumor volume on MRI should be defined as the GTV with no respect for the surrounding edema. No extra margins are required for the creation of clinical target volume (CTV) or planning target volume (PTV) for frame-based SRS, while a debated margin of 1 to 2 mm

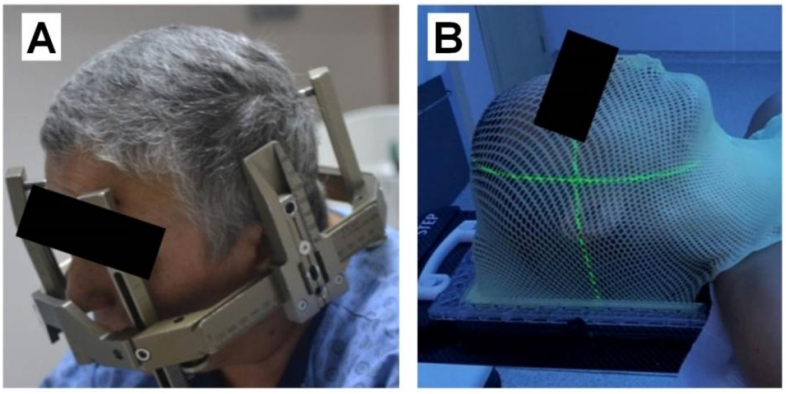


Fig. 1. Patient immobilization and setup positioning during the treatment of patients with (A) Gama-knife-based, and (B) Linear accelerator- based stereotactic radiosurgery with a non-invasive frame

might be added to GTV for the definition of PTV for frameless SRS. The same contouring principles apply to the cases scheduled to undergo preoperative SRS, as well. The surgical cavity should be defined as the CTV for postoperative SRS applications, while a 2 mm margin encircling the surgical cavity at all dimensions ought to be considered for the creation of the PTV, which may efficiently reduce the risk for marginal misses, local recurrences, and leptomeningeal spread [13,14].

2.4 Contouring of Organ at Risk Volumes

An explicit outline of the OARs is of vital importance for an efficient and less toxic intracranial SRS arrangement. Therefore, the brain, brainstem, hippocampi, hypophyseal gland, optic chiasm, optic nerves, and cochlea should be contoured as the OARs for a typical intracranial SRS application (Fig. 2). The practical recommendations stipulated below ought to be thoroughly appreciated during the process of OAR contouring for the guaranteed safety of the treatment procedure:

Brain: The brain is the division of the central nervous system which comprises the entire structures which reside in the skull. The cranial and caudal limits of the brain should be defined as the inner border of the vertex and the lower border of the foramen magnum, or alternatively, the upper border of the first cervical vertebrae for the contouring purposes.

Brainstem: The brainstem is the distal part of the brain made up of the midbrain, pons, and medulla oblongata with its unique arrangement and functions. The superior border of the posterior clinoids and the lower border of the foramen magnum are respected as the cranial and caudal anatomical guides of the brainstem. Considering the subsections, the midbrain is

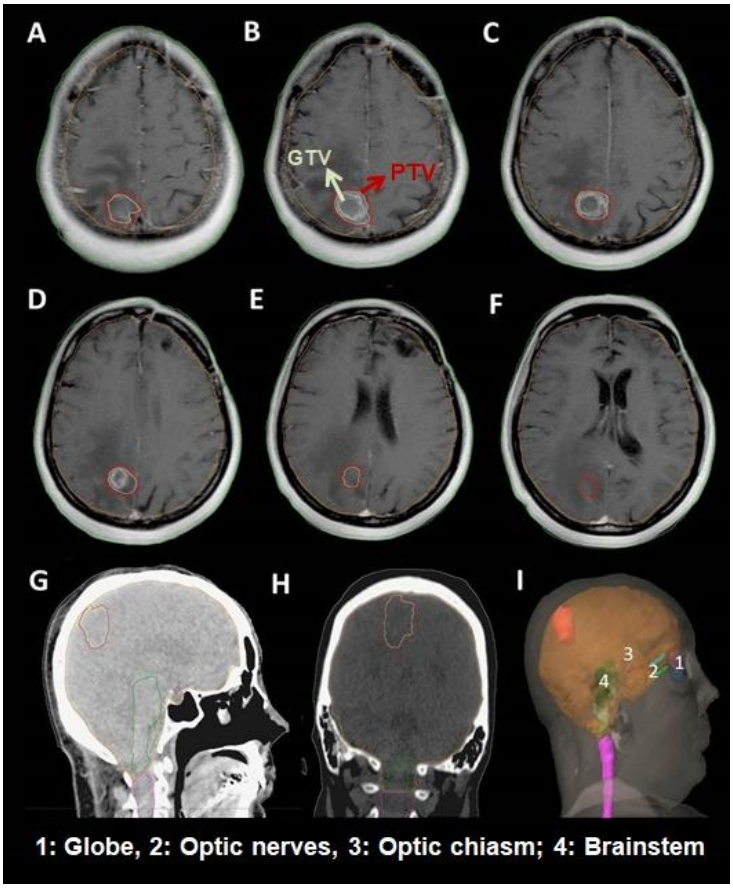


Fig. 2. Target volume and organs at risk contouring: GTV: Gross tumor volume, and PTV: Planning target volume; 1:Optic chiasm; 2:Optic nerves; 3: Brainstem

approximately the upper 20 mm portion of the brainstem, which rests just inferior to the third ventricle. The most voluminous portion of the brainstem, namely the pons, is about a 25-30 mm structure that is distinguished from the superiorly located midbrain and inferiorly located medulla by the superior and inferior pontine sulci, respectively. The medulla oblongata is the most inferior portion of the brainstem that extends between the pons and spinal cord. The most inferior border of the foramen magnum is the anatomical landmark that marks the border of the amalgamation of the medulla oblongata and the spinal cord [15]. The brainstem represents one of the key centers for the regulation of the vital functions, such as blood pressure, heart rate, breathing, and many other critical ones by lodging multiple cranial nerve nuclei. The synchronized utilization of the axial and sagittal MRI images is strongly advised to improve the accuracy of the brainstem delineation procedure.

Hippocampi: The **hippocampus** (Cornu Ammonis**)** is a vital segment of the human brain which applies indispensable capacities in information processing, cognition, and the reproductive cycle. The hippocampus lies in the hippocampal sulcus of the temporal lobe immediately below the floor of the temporal horn of the lateral ventricle and has appearances that are suggestive of a seahorse in coronal section. Although the patient's age and various disease conditions may be alter the hippocampus volume, usually it is measured to be in the range of 2.8 to 4.0 cm^3. The hippocampus is comprised of three parts: 1) Anterior segment or the head; [2] Intermediate segment or the body; and [3] posterior segment or the tail. The tail of the hippocampus follows the upwardly curving lateral ventricle, while its head is located just posterior to the amygdala with its tail lodging in between. The hippocampus is best discriminated on the coronal MRI scans angled perpendicular to the long axis of the hippocampal body. Delineation process of the hippocampus ought to be performed on axial T1-weighted MRI sequences by focusing on the T1-hypointense signals medial to the temporal horn due to the gray matter preponderance in the hippocampus,. Delineation should be initiated at the level of the most caudal extent of the crescent-shaped floor of the temporal horn and continued along the medial edge of the temporal horn postero-cranially. The edge of the T1-hypointensity up to the ambient cistern should be taken as a reliable reference for the accurate delineation of the medial border of the hippocampus. Likewise, the uncal recess of the temporal horn may usefully assist in distinguishing the hippocampus from the antero-superiorly located gray matter of the amygdala. The posterior and cranial portion of the hippocampus, namely the hippocampal tail, is delineated as the tissue located just anterior and medial to the atrium of the lateral ventricle. Contours should be terminated at the lateral edges of the quadrigeminal cisterns, prior to the emergence of the crus of the fornix [16,17].

Hypophysis: The hypophysis is a pea-sized (craniocaudal up to 12 mm) endocrine gland that sits at the base concavity of the sphenoid bone skull: sella turcica or Turkish saddle. Anatomically, hypophysis is located just below the hypothalamus and optic chiasm. The hypophysis has embryologically and functionally two disparate parts, precisely the anterior and posterior hypophysis, which together with its nexus to the hypothalamus embodies the major endocrine organ of the body. For delineation purposes, though the borders of the pituitary fossa are well defined, it should be retrieved that it may be challenging to accurately define the exact borders of the hypophysis on CT sections. The borders of the pituitary gland can be defined best in the sagittal view of the contrast-enhanced MRI sections. The inner part of the sella turcica can be used as a surrogate anatomical bony structure best distinguished utilizing the bone 1500/950 or soft tissue 350/50 WL/WW on CT [18]. In summary, the anatomical landmarks for the delineation of the hypophysis are as follows: Laterally the cavernous sinuses; inferiorly the sphenoid sinus housing the hypophyseal concavity; superiorly the diaphragma sellae, optic chiasm, and the hypothalamus where hypophysis unites to the brain via its stalk; anteriorly the sphenoid sinus (surgical corridor for the trans-sphenoidal surgery); and posteriorly the dorsum sellae, posterior intercavernous sinus, pons, and the basilar artery, individually.

Optic chiasm: The avoidance of the excess doses to the optic chiasm is of utmost importance for the protection of vision during the conventional radiotherapy and SRS procedures. The optic chiasm is the X-shaped neural formation where the left and right optic nerves converge. The optic chiasm is placed in the forebrain just ventral to the hypothalamus. Because of its position, the optic chiasm directly contacts anteriorly with the cerebrospinal fluid within the subarachnoid space and posteriorly within the third ventricle. For the delineation purposes, it is compulsory to recognize that the

optic chiasm lies paradoxically over the body of the sphenoid bone (typically above the diaphragm sellae) rather than its natural but rarely observed sulcus chiasmaticus location. The relative position of the chiasm over the sellae turcica is variable: 1) above the diaphragm sellae in 79%, 2) above the tuberculum sellae in 12%, and 3) above the dorsum sellae in 4% of cases [19]. For measurement purposes, the optic chiasm has a transverse diameter of 10-20 mm, an anteroposterior width of 4-13 mm, and a thickness of 3-5 mm [19].

Optic Nerves: The optic nerves are neural structures consisting chiefly of neural fibers derived from the retinal ganglionic cells that carry the visual information from the retina to the optic chiasm and the suprachiasmatic central visual pathways. Anatomically, the optic nerves have four conventional segments: 1) Intraocular segment posterior to the retina, 2) Intraorbital segment (20 to 30 mm), 3) Intracanalicular segment and (d) intracranial segment (17 ± 2.4 mm) which finally fuses with the optic chiasm [20]. of note, the orbital segment of the optic nerve has a somewhat sinuous course that enables the movements of the eyeball in the orbital cavity.

Cochlea Cochlea: First described by Eustachi in 1564, the cochlea is a shell-shaped, fluid-filled bony spiral with nearly 2.5 and 2.75 turns around the modiolus. The cochlea is settled in the petrous pyramid of the temporal bone. Grossly, the external diameter of the cochlea varies approximately from 5 mm at its apex and 9 mm at its base. Even though the cochlea isn't legitimately prominent on CT scans due to its small size and the deep situation in the temporal bone, yet its volume can be circumscribed as a bone cavity on CT images where it rests [19, 21]. For delineation goals, the anatomic limits of the cochlea can be marked as follows: cranially the petrous apex of the temporal pyramid; caudally the carotid canal; medially the temporal pyramid; laterally the medial wall of the tympanic cavity; anteriorly the superior and anterior surface of the petrous bone; and posteriorly the anterior aspect of the internal auditory canal. A CT scan window width of 1,600 HU and a center scan level at 450 HU may serve as very assistive in the precise delineation of the cochlea.

2.5 Ideal Dose Selection

The ideal SRS doses are essentially selected by accounting for the size and closeness of the BM to the neighboring healthy tissues. For BMs, the current broadly comprehended maximum tolerated doses (MTD) for BM were first discovered by the RTOG 90-05 dose-escalation trial [22]. As indicated by the results of this milestone research, 24, 18, and 15 Gy were authenticated as the standard dose suggestions for lesions ≤20, 21-30, and 31-40 mm, separately. Nonetheless, an ensuing retrospective analysis by Shehata et al. surveying the sound SRS dose in patients with 468 BMs (≤ 20 mm) unsealed that the SRS doses >20 Gy were linked with a firm inclination for increased grade 3-4 neurotoxic event rates (5.9% vs. 1.9%, p=0.078), with no meaningful tumor control profit [23]. Thus, currently, a prescription dose of 20 Gy seems to offer the most expedient tumor control rates with more fair severe toxicity rates over the regimens using 24 Gy. Albeit the aforementioned doses have been approved for single-dose SRS, yet, fractionated stereotactic RT (FSRT) applications utilizing doses in the range of 24-30 Gy in 3, 30-35 Gy in 4-5, and 35-40 Gy in 7-10 fractions might be sensible alternatives for larger BMs or those in eloquent locations like the brainstem or thalamus, without sacrificing the excellent tumor control rates witnessed with single-dose SRS protocols [9]. Of note, the above-mentioned dose selection criteria and fractionation schemes are also relevant in the setting of preoperative SRS [14, 24-27].

As of now, the lack of universally welcomed care standards for the management of BM following neurosurgery, the conservative strategy sojourned to be WBRT up to this point. In any case, various researchers have examined the results of tumor cavity SRS, based on the known substantial risk of cavity local recurrences after surgical resection alone, with the ultimate goal of improving the cavity control rates with contemporaneous avoidance of the deleterious consequences of WBRT, including the neurocognitive decline [28-33]. The ideal doses and the definite safety margins for the creation of the PTV have not been settled yet for successful postoperative SRS applications. The local control rate was reported to be 80% in a series of 37 BM patients treated with 24 Gy (8 Gy per fraction) with 2 to 3 mm margins in every direction around the cavity [15]. Minniti et al. in a cohort of 101 patients with tumor cavities >3 cm (all single BM), reported that the addition of a 2-mm CTV to PTV margin was connected with excellent 1-year (93%) and 2-year (84%) local control rates for FSRT of a total dose of 27 Gy given in three fractions [34]. Accordingly,

acknowledging the accessible literature, it is judicious to counsel 24-27 Gy in three fractions for patients undergoing postoperative SRS, that is prescribed to a volume encompassing the resection cavity by 2 to 3 mm, preferably 2 mm.

2.6 Dose Prescription Isodose Lines

Albeit each SRS device has own dosimetric characteristics for treatment planning procedures, yet, the vast majority of the key fundamental principals are shared by most of them. The typical GK and LINAC-based SRS treatment plans employ multiple isocenters which create multiple spherical isodose lines and ensuant high and non-uniform dose distributions in the designed TV, despite the accessibility of the more commonly used mono-isocentric plans in the modern LINAC-based SRS applications [35]. In a typical LINAC-based SRS plan, the dose is usually prescribed to 70-80% isodose line covering the TV which stipulates the percentage of the maximum dose that encloses all margins of the TV. Greater dose inhomogeneities in the TV and an immediate initial dose fall-off outside the prescription isodose represent the characteristics of GK-SRS as a consequence of the prescription of the dose to the 50-80% isodose lines. The regular debates on the obstacles of the dose uniformity of conventional radiotherapy plans are worthless and not pertinent for SRS, as the core intention of any SRS plan is to spare the OAR convincingly rather than offering homogenous dose distributions in the TV [35].

2.7 Treatment Plan Assessment

The most basic and useful tool for the assessment of any SRS or FSRT plan is the dose-volume histogram (DVH) which supplies essential metric information in deciphering the plots of the volume covered by each dose level and affords a common scientific language among the SRS researchers (Fig. 3 and 4). Coverage levels of the TV, hot and cold spots, doses received by the distinct volumes of interested OARs, and the aptness of the plan can be efficiently and precisely surveyed by DVH analysis, as well as through comparisons between several plans. Besides this key evaluation procedure, there are additional but more intricate tools for the plan quality evaluations, such as the conformity index, Paddick conformity index, homogeneity index, selectivity, and gradient index (Table 1) [7].

2.8 The RTOG Plan Quality Indices

The investigators of the RTOG proposed three popularly utilized metrics to portray the SRS plan quality. The first metric was the conformity index (CI), which was appointed as the volume of a prescription isodose line divided by the TV [35, 36]. Although this straightforward metric is a perfectly outlined measure of how well the prescribed dose adjusts and covers the TV [37], yet, regrettably, it does not provide volumetric information about the peculiar levels of the dose received by the encompassing healthy tissues. The ideal CI value is 1, indicating that the prescription isodose line fits one-to-one with the TV without spread-out doses past the TV. Consequently, CI values >1 allude to over-coverage of the TV with useless high-dose volumes past the predicted TV. Likewise, a CI value <1 indicates insufficient TV coverage by the isodose line, implying that some parts of the tumor miss the prescribed dose, which is indeed irrelevant. According to the RTOG categorization for CI protocol compliance, plans with a CI value between 1.0-2.0 are labeled as not deviating; between 2.0-2.5 or 0.9-1.0 as minorly deviated; and>2.5 or <0.9 as majorly deviated, and in this manner, inadmissible.

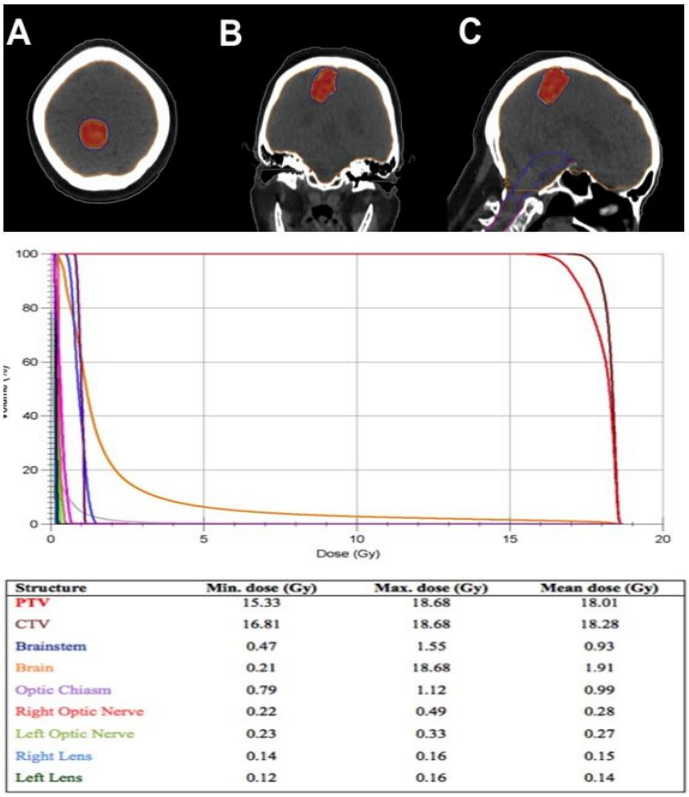
The second proposed index is the coverage quality, Q: the ratio of minimum dose in the TV to the prescription isodose [38]. Plans with the 90% isodose line covering the TV do not deviate from the protocol, while plans with ≥ 80% and < 80% isodose line coverage are categorized as minorly and unacceptably or majorly deviated, respectively.

The third RTOG metric is the homogeneity index, HI [38], that is the ratio of the maximum point dose in the TV to the prescription isodose line. Plans with a HI value ≤ 2 are affirmed to not deviate from the protocol, while minor and unacceptable major deviations are defined as the HI between 2 and 2.5 and HI > 2.5, individually.

2.9 Alternative Conformity Indices

Dedicating to afford an objective method for the plan quality comparisons and the dismissal of “false scores” related to the CI, Paddick introduced an alternative CI in 2002; $CI_{Paddick}$ [39]. This index builds on the criticism of the CI that the overlap of the volume receiving the prescription isodose and the TV is not taken in to account. This new CI is calculated as $CI_{Paddick}$ =TVPIV2 / (TV2 x VPD), where TV is the target volume, TVPIV is the TV covered by the

prescription isodose, and VPD is the total volume covered by the prescription isodose. $CI_{Paddick}$ has an ideal value of 1 and the plan's quality diminishes with lower values. The $CI_{Paddick}$ and CI are inversely related indices which can be expressed as $CI_{Paddick}$ = 0.933/CI



Structure	Min. dose (Gy)	Max. dose (Gy)	Mean dose (Gy)
PTV	15.33	18.68	18.01
CTV	16.81	18.68	18.28
Brainstem	0.47	1.55	0.93
Brain	0.21	18.68	1.91
Optic Chiasm	0.79	1.12	0.99
Right Optic Nerve	0.22	0.49	0.28
Left Optic Nerve	0.23	0.33	0.27
Right Lens	0.14	0.16	0.15
Left Lens	0.12	0.16	0.14

Fig. 3. LINAC based stereotactic radiosurgery plan: A) Axial; B) Coronal; C) Sagittal view; and related dose-volume histogram and dose parameters

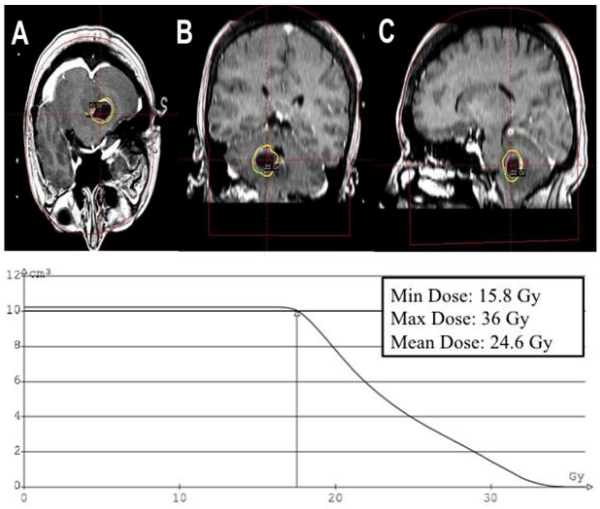


Fig. 4. Gama-Knife stereotactic radiosurgery plan: A) Axial; B) Coronal; C) Sagittal view; and related dose-volume histogram

Table 1. Frequently used indices for the assessment of the stereotactic radiosurgery and fractionated stereotactic radiotherapy plans

Dose plan indices	Formula	Acceptable value
Conformity index (CI)	PIV/TV	1-2 (0.9-3.5)
Paddick conformity index ($CI_{Paddick}$)	TV_{PTV}^2/TV × PTV	1
Selectivity index (SI)	TV_{PIV}/PIV	1
Gradient index (GI)	$PIV_{X\%}/PIV_{(X/2)\%}$	<3
Homogeneity index (HI)	D_{max}/PD	1(1.1-2.5)
Coverage (Q)	D_{min}/PD	0.9-1
CI_{Lomax}	TV_{PIV}/TV	0-1

Abbreviations: TV: Target volume; PIV: Prescription isodose volume; TVPIV: Volume of prescription isodose in the target; Dmax: Maximum dose point in the treatment volume; PD: Prescription dose; X: Isodose which carries the prescription isodose; X/2: Isodose which carries 50% of the prescription isodose; Dmin: Minimum dose point in the treatment volume.

Lomax and Scheib urged another alternative CI, CI_{Lomax}, which is a modification of the SRS plan quality criterion originally introduced by the Saint-Anne, Lariboisiere, and Tenon groups for SRS of arteriovenous malformations [40]. CI_{Lomax} is calculated as CI_{Lomax}= TVPIV / TV, where TVPIV is the target volume covered by the prescription isodose, and TV is simply the target volume itself. CI_{Lomax} shows the proportion of the target volume that receives the prescription dose as a minimum dose. This index can range between 0 to an optimum value of 1 and is the square root of the geometric overlap ratio that is used in the $CI_{Paddick}$.

Gradient index (GI) defines the dose fall-off sharpness around the target volume TV which is calculated by dividing the volume receiving 50% of the prescribed dose to the volume of the prescribed isodose line. Any plan with an excellent CI does not always indicate an astounding dose distribution for the OARs if they receive irrelevant doses. Henceforth, despite the perfect conformity, an optimal dose fall-off is likewise requisite for minimizing the complication hazards. In this sense, GI can be accepted as an indicator of the ideal prescription isodose with the steepest dose fall-off [37].

Selectivity index (SI), or just selectivity, is another index for a thorough evaluation of any SRS plan. While CI assesses the SRS plan in a way whether the chosen isodose conforms to the three-dimensional target volume with high doses restricted to the target. SI deals with the fact whether the integral dose received by the surrounding tissues is as low as could reasonably be supposed. Plan selectivity is calculated as; SI= VPD × TV / VPD, where VPD is the total volume receiving the prescribed dose, and TV is the target volume. An ideal SRS plan should have SI of 1 while any value > 1 and < 1 refers to over- and under-treatment, individually.

The counseled parameters and their limits for a standard SRS plan evaluation regarding the TV coverage and OAR limits are exhibited in Tables 2 and 3.

Table 2. Recommended specifications for stereotactic radiosurgery and fractionated stereotactic radiotherapy plan assessments

Parameter	No variation	Minor variation (Acceptable)	Major variation (Unacceptable)
Target coverage	The 90% isodose line (90% of the PD, not TD) completely covered target)	80% isodose line covers the target	80% isodose line does not cover the target
Dose QA (lesion size, PD)	2.0 cm: 20 Gy 2.1-3.0 cm: 18Gy 3.1-4.0 cm: 15Gy	- - -	- - -
Dose homogenity (MD/PD)	≤2	2-2.5	>2.5
Dose conformity (PIV/TV)	1.0-2.0	0.9-1.0 or 2.0-3.5	<0.9 or >3.5

Abbreviations: PD: Prescription dose; TD: Total dose; QA: Quality assurance; MD: Maximum dose; PIV: Volume of prescription isodose line; TV: Target volume.

2.10 Quality Assurance

Because notably larger doses are prescribed and delivered per fraction of SRS and FSRT, any trivial deviation in circumscribing the target volume or dose delivery can precipitate major errors. To minimize such errors, SRS quality assurance (QA) ought to be more meticulous than the standard radiotherapy. Numerous organizations have reported several SRS QA guidelines to preclude likely errors [41-48]. The first report from the American Association of Physicists in Medicine (AAPM) for explicit QA of SRS treatments was published as Task Group 42 (TG-42) in 1995 [49] and updated reports adjusted for cutting edge innovative technologies have become accessible with the latest published guideline, namely the TG-142 [43]. Additionally, the RTOG has also published SRS guidelines [50]. QA recommendations for the overall performance of all SRS equipment consist of two steps; the periodical general QA (daily, monthly and annually), and per patient based specific QA (pretreatment calibration and preparation), separately.

General QA procedures necessitate being set periodically to establish equipment status and performance, including the target localization, basic dosimeter, treatment planning, output calibration, and dose delivery QAs. A comprehensive QA program obeying the reported international recommendations should be arranged to periodically check and adjust all items, particularly the ones with relatively higher failure rates with resultant serious consequences. Many of the errors in radiation oncology are not prompted by malfunctions in the treatment devices, assistive equipment, and software; rather, they are workflow and process ancillary failures. Hence, end-to-end tests are commonly used to measure the overall precision of the RT chain, except for the patient-specific factors. End-to-end testing, determining any dosimetric or mechanical problems, is one of the best means to measure the overall

Table 3. Recommended dose tolerance limits for stereotactic radiosurgery and fractionated stereotactic radiotherapy

Organs	Reference	Fractions (n)	Volume (cc)	Volume (%)	Volume limit (Gy)	D_{max} limit (Gy)
Brainstem	103	1	1		10	15
	103	1	1		18	8
	Traditional	1				23
	103	3				31
	103	3				
	103	5				
Optic chiasm	104	1	0.2	100	15	[a]15
and nerves	105	1	0.2		20	13
	105	1			20	12
	105	1				11
	103	1				[b] 10
	103	3				19.5
	103	3				25
	103	5				
	103	5				
	105	5				
Cochlea	103	1				12
	103	3				20
	103	5				27.5
Brain	105	5		100	20	
Lens	105	1				3
	105	2				6
	105	3				7
	105	5				7

Abbreviations: Dmax: Dose maximum; FSRT: fractionated stereotactic radiotherapy; SRS: stereotactic radiosurgery.a: 77% probability of neuritis if Dmax >15Gy
b: No risk for optic neuritis if Dmax <10Gy

Table 4. Summary of available stereotactic radiosurgery tests reported in The American Association of Physicists in Medicine Task Group report (AAPM-TG-142)

Tests of mechanic and dosimetric requirements	Daily	Monthly	Annual
Laser localization	< 1-mm		
Distance indicator	< 2-mm		
Collimator size	Indicator < 1-mm		
Stereotactic interlocks	Functional		
Laser localization	< 1-mm		
Typical dose rate output constancy		2% at SRS dose rate, MU	
Treatment couch position indicators		< 1-mm/0.5◦	
Localizing Lasers		< 1-mm	
SRS arc rotation mode (range 0.5-10 MU/deg)			MU set vs. delivered: 1 MU or 2%
X-ray MU linearity (output constancy)			Gantry arc set vs. delivered 1% or 2%
Coincidence of radiation and mechanical isocenter			5% (2 - 4 MU) 2% (5 MU)
Stereotactic accessories, lockouts, etc.			1 mm from baseline
End to end localization assessment / dosimetric evaluation using SRS frame or IGRT system			< 1-mm < 2%
MV and kV imaging			
Positioning/repositioning	< 1-mm		
Spatial linearity1 (x and y) (single gantry angle)		< 1-mm	< 1-mm
Imaging and treatment coordinate coincidence (4 cardinal angles)		< 1-mm	< 1-mm
Cone-beam CT (kV and MV)			
Positioning/repositioning	< 1-mm		
Imaging and treatment coordinate coincidence (single gantry angle)		< 1-mm	< 1-mm
Geometric distortion			< 1-mm

[a]Optical distance indicator check with a pointer compared lasers and source skin distance;
[b]Tolerance is summation of total for each width or length and asymmetric jaws should be checked at settings of 0.0 and 10.0.;[c]Dose monitoring as a function of dose rate.
[d]Lateral, longitudinal, and rotational.
[e]All tests must cover i) geometric accuracy, (ii) dosimetric accuracy, and (iii) treatment reproducibility.
[f]kV imaging refers to both 2D fluoroscopic and radiographic imaging.
[g]Scaling measured at SSD typically used for imaging.Abbrevitions: SRS: Stereotactic radiosurgery, MU: Monitor unit(s), IGRT: Image-guided radiotherapy, MV: Million volts, kV: Kilovolts, CT: Computerized tomography

success of SRS therapy. In this way, most of the small errors that occur by performing end-to-end tests through phantoms counseled by AAPM Task Group 142 can be determined cumulatively. Table 4 provides a summary of the tests in AAPM TG-142.

The last but not the least component of an efficinet QA program is the patient-specific pre-treatment QA. The goal of the patient-specific QA is to assure that the treatment devices and its assistive components are suitably adjusted and operating, and the treatment parameters are best-fit calibrated and set before and during the treatment. Patient-specific plan checks ensure the fidelity of the overall system from the treatment planning to the dose delivery steps by conceiving a patient-specific treatment planning capacity to the facility, transferring plans to the data network, and checking the imaging systems and auxiliary equipments., To increase the accuracy of the QA procedure, it is strongly advised to formulate a clinic-specific checklist for all tests documenting the measurements in

tissue equivalent phantoms, such as the dose calibration, percent depth doses, relative dose exit factors, and cross-beam profiles [42,44].

3. CONCLUSION

The SRS and FSRT have progressively perceived as highly efficient and less toxic treatment options than the conventional WBRT for the treatment of the patients presenting with single or multiple BMs. Nevertheless, the process of the SRS planning and quality assurance is unquestionably challenging, considering the availability of numerous planning systems and treatment machines with completely distinct operational features, as well as the primary intention of the SRS and its relative delivery timing to the other treatment modalities, like the neurosurgical BM resection and/or the systemic therapies. Consequently, the success of the SRS or FSRT applications rely upon the cooperation of the SRS team comprised of at least skilled radiation oncologists, radiotherapy physicists, radiobiologists, radiologists, and nuclear medicine physicians who stringently adhere to the unique specifications of the planning systems, treatment machines, and the universally apprehended SRS/FSRT guidelines.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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