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Physics Contribution

Dose Gradient Index for Stereotactic Radiosurgery/Radiation Therapy

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Purpose: Steep dose falloff outside of tumors is a hallmark of stereotactic radiosurgery (SRS) and radiation therapy (SRT). Dose gradient index (DGI) quantifies the dose drop off. Tables of DGIs versus target volumes have been published for body sites, but none is available for brain. This study recommends guidelines for DGIs for brain SRS/SRT treatments based on clinical CyberKnife (CK) cases.

Methods and Materials: Four hundred ninety-five plans for patients with central nervous system tumors treated with CK at our institution between March 2015 and May 2018 were analyzed. The CK treatment planning system MultiPlan was used for planning. SRS/SRT plans were stratified into 6 groups by tumor size (Group I [0-1 cm^3], II [1.0-3.0 cm^3], III [3.0-5.0 cm^3], IV [5.0-10.0 cm^3], V [10.0-15.0 cm^3], and VI [15.0-40.0 cm^3]). Ideal and minimally acceptable DGIs were determined for each size group. To evaluate the effect of target shape on DGI criteria, the plans were divided into 4 target shape groups: (1) homogeneous shape (circular), (2) adjacent to radiosensitive organs at risk (adjacent), (3) irregularly shaped (irregular), and (4) multiple target plans (multilesion). The mean for each target size group was defined as the ideal DGI. Minimally acceptable DGI criteria are specified to reject the lowest 10% of cases.

Results: The minimal acceptable DGIs were 83 (Group I), 72 (II), 65 (III), 58 (IV), 52 (V), and 35 (VI). The ideal DGI is designated to evaluate SRS/SRT plans for homogeneous circular lesions, whereas minimal DGI is chosen to assess the plans for irregular, adjacent to organs at risk, and multilesions. SRS/SRT plans with higher DGI values are correlated with lower irradiated normal tissue volumes.

Conclusions: This study provides a table of DGIs for brain SRS/SRT treatments as a tool for assessing the quality of intracranial SRS/SRT plans. DGI guidelines support SRS/SRT planning that results in lower risk of radionecrosis.

Introduction

Radiation therapy has played a vital role in the treatment of intracranial tumors over the past several decades. It has been demonstrated to increase patient survival rates and improve quality of life.[1,2] The conventional treatment technique for both identifiable brain metastasis and prophylaxis for microscopic disease is stereotactic radiosurgery (SRS)/stereotactic radiation therapy (SRT) with or without whole brain radiation therapy.[3] SRS provides accurate delivery of a high dose of radiation to a target in a

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single fraction while sparing the surrounding normal tissue. If such treatment is fractionated into 2 to 5 fractions, this treatment is referred to as SRT. The conditions most commonly treated with SRS include arteriovenous malformations, vestibular schwannomas, meningiomas, recurrent gliomas, and metastatic brain tumors. SRS and SRT allow for more localized delivery of radiation, which may reduce concerns regarding the acute and late toxicity profile associated with whole brain radiation therapy. This prompted the development of several prospective studies designed to demonstrate the effectiveness of SRS treatments for patients with intracranial lesions.[4-7]

The crucial component of SRS/SRT is precise delivery of the radiation dose to the target conformally with rapid dose falloff into the surrounding normal tissues. The conformity index (CI) quantifies how closely the radiation prescription (Rx) dose conforms to the size and shape of the target.[8] Dose gradient index (DGI) quantifies the dose falloff outside of the target.[9] Historically, the conformity of the dose was the key component of SRS/SRT. The guidelines for a conformity parameter were initially proposed in 1993 by the Radiation Therapy Oncology Group (RTOG)[10] and are described in report 62 of the International Commission on Radiation Units and Measurements.[11] The proposed conformity values are widely used by radiation oncology centers as a valuable quantitative evaluation tool to assess the quality of a treatment SRS/SRT plan. However, to fully evaluate plan quality, DGI is vital to ensure optimal dose falloff outside of the target. Because the radiation oncology society realized the importance of a dose falloff parameter (DGI), guidelines for DGIs versus target volumes for body sites were published.[12,13]

The most common complication from SRS/SRT radiation therapy is radionecrosis (RN), resulting from dose spreading into significant volumes of normal brain tissues.[14] Many studies associate the risk of RN with volumes of normal tissue brain irradiated to the doses 12 Gy (V12Gy) for SRS and 24 Gy (V24Gy) for SRT.[15-17] V12Gy and V24Gy are shown to be predictive factors of the risk of RN.[15-17] Predictive factors associated with the development of brain RN are both patient related (tumor location, diameter, previous radiation, and sex) and treatment related (total dose, number of isocenters treated, prescription isodose volume, conformality and heterogeneity indices, and volume of brain receiving a specific dose).[15-20] Our study shows that DGI of SRS/SRT plan directly correlates with the irradiated normal tissue volumes relevant to adverse effects. Therefore, there is a need to evaluate the dose spread into normal tissue brain to reduce the toxicities associated with it. Nevertheless, DGI guidelines for brain for SRS/SRT are lacking in the literature. The goal of this study is to suggest DGI guidelines versus tumor size based on our experience in planning 495 SRS/SRT patients. Clinical examples of DGI guideline applicability are presented for each target shape in supporting information.

Methods and Materials

CyberKnife unit

CyberKnife (CK) (M6 unit) robotic radiosurgery unit was used in this study. It consists of a 6-MV linear accelerator mounted on a robotic manipulator and equipped with 2 types of collimators: the fixed-cone collimator and the Iris variable-aperture collimator. Both types of collimators are available in 12 sizes: 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 50, and 60 mm in diameter measured at a nominal treatment distance of 800 mm.

Patient population

Four hundred ninety-five patients treated with CK using SRS/SRT techniques at our institution between March 2015 and May 2018 were analyzed for this study. The patients were excluded from the study if planning target volume (PTV) was larger than 40 cm^3. The patient population was made up of 248 cases of secondary malignant neoplasms (MNs) of brain, 108 benign neoplasms (BNs) of cerebral meninges, 54 cases of arteriovenous malformations of cerebral vessels, 50 BNs of cranial nerves, 10 BNs of pituitary gland, 10 MNs of cerebral meninges, 10 other brain neoplasms, and 5 cases of MNs of brain, unspecified (Fig. 1a). Dose ranged from 1500 to 3000 cGy with a mean (median) dose of 1981 (2000) cGy for SRS and 2508 (2500) cGy for SRT. The number of fractions for SRT ranged from 2 to 5. The patients were separated into 6 groups with respect to tumor sizes (Group I [0-1 cm^3], II [1.0-3.0 cm^3], III [3.0-5.0 cm^3], IV [5.0-10.0 cm^3], V [10.0-15.0 cm^3], and VI [15.0-40.0 cm^3]) (Table 1). The distribution of the patients with tumor size is presented in Figure 1b. The selected lesions were intended to represent the wide range of target volumes between 0.1 and 40 cm^3.

Traditionally, to evaluate the effect of tumor shape and location on DGI, the SRS/SRT plans were also divided into 4 groups (Fig. 1c). This specification was done manually based on visual inspection. These groups include homogeneous lesions located in the absence of adjacent radiosensitive structures (circular); irregularly shaped lesions (irregular) with the only organ at risk (OAR) nearby being the nontarget brain tissue; lesions located in proximity to radiosensitive structures (adjacent); and multilesion cases that were treated in the same SRS/SRT plan (multilesion). The majority (77%) of the multilesion plans are 2-lesion plans, 20% are a 3-lesion plans, and the remaining 3% are 4-lesion plans.

Treatment planning process

All patients were simulated in the supine position and immobilized with a reinforced thermoplastic mask (Klarity Medical). Computed tomography (CT) images were

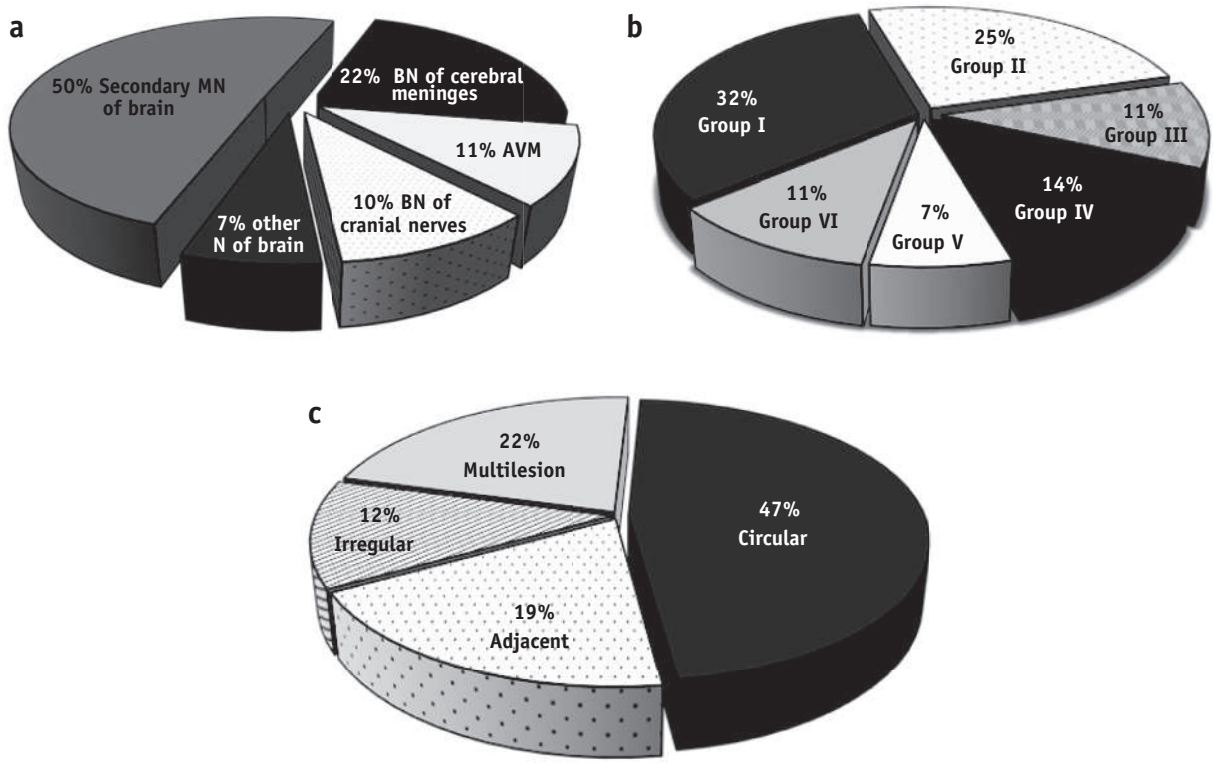

Fig. 1. The distribution of patient population treated with stereotactic radiosurgery/radiation therapy with CyberKnife in the period of March 2015 to May 2018 (a) versus diagnosis, (b) versus target size, (c) versus target shape.

acquired with 512 × 512-pixel resolution and slice thickness of 1.25 mm. The planning CT scans were coregistered with T1- and T2-weighted postcontrast magnetic resonance (MR) images with 1 mm slice thickness using a mutual information-based algorithm implemented in MIM (Version 6.7). The gross tumor volume (GTV) was defined as an enhanced lesion on the MR image by a neuro-oncologist or radiation oncologist. GTVs and OARs were delineated based on the MR imaging and approved by neurooncologist and radiation oncologist. The GTV was expanded to a PTV with a 0 to 2 mm margins. Typically, a 0 mm margin was used for benign lesions and 1 to 2 mm for malignant lesions.

The OARs delineated for all brain case patients included eyes, optic nerves, optic chiasm, optic pathway (optic nerves and optic chiasm), brain stem, and spinal cord. Planning risk volumes for spinal cord, brain stem, and optic pathway were created by adding an additional 2 mm to account for uncertainty related to the delivery of radiation to the target.

Table 1 Distribution of patients with respect to tumor size

Patient group	Tumor size (cm^3)	Mean (median) (cm^3)	No. of patients
Group I	0.1-1.0	0.51 (0.50)	157
Group II	1.0-3.0	1.82 (1.73)	123
Group III	3.0-5.0	4.06 (4.04)	56
Group IV	5.0-10.0	7.07 (7.06)	68
Group V	10.0-15.0	12.34 (12.26)	36
Group VI	15.0-40.0	24.23 (24.31)	55

The treatment planning process was carried out with the CK treatment planning system Multiplan, version 5.3.0 (Accuray Inc.). Ray-Tracing algorithm was used for all calculations due to homogeneity of the brain tissue. All plans were set up with Head_Iris-Fixed treatment anatomy, full path set, and 6-dimensional (skull)-tracking method. The beam direction was restricted to never intersect with the eye OAR unless the target is located near an eye. If the lesion was close to the eyes, beams were set up as exit only.

The sequential planning method was used for all plans. The initial setup of the plan involved the choice of collimator, number of monitor units (MUs) per beam (300 MUs) and per node (450 MUs), upper bounding constraint for the PTV, and PTV coverage goal. Typically, 4 shells around the target were used to achieve a sharp dose gradient. The plans for PTVs with volumes less than 0.5 cm^3 were generated with a single fixed-cone collimator. CK treatment plans were always prepared using a single fixed collimator to avoid collimator exchange time. The plans for larger lesions were generated with an Iris collimator of multiple aperture sizes to minimize the total MUs and treatment beams. However, the 5 mm fixed-cone and Iris collimator were not used for the treatment planning owing to the concern about the relatively large uncertainty on the output and geometry reproducibility. The aperture size of the collimators depended on the tumor size, centricity, location,

and proximity of the target to critical OARs. Additional upper bonding constraints were set up for critical OARs for the cases in which lesions were adjacent to critical OARs. Plan optimization was performed by dose volume lower limit treatment planning algorithm, which selects beam weights for each direction and minimizes a series of linear cost functions sequentially until the final solution is achieved. The final calculation of the plans was performed with high resolution and fully open calculation grid volume, encompassing the entire CT image.

Prescription dose and OAR tolerance doses

SRS prescription doses were prescribed according to size of the lesions, which varied from 1500 to 2200 cGy, according to RTOG 9508.[18] The selection of SRS or SRT regimens was influenced by the target size and location (Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2019.11.408). Ideally 5 cm^3 tumor volume is a good clinical cutoff for SRS treatments. Indeed, 91% of the SRS and 44% of SRT cases corresponded to the group with tumor size of $\leq$5 cm^3 (Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2019.11.408). The main reason for the SRT regimen for tumor volumes <5 cm^3 was targets being adjacent to critical OARs. Only 4 out of 95 adjacent target cases were treated as SRS, and the rest were SRT plans. All dosimetric constraints for critical OARs were adapted from TG101,[21] and the constraints for normal brain tissue were adapted from Bloniger et al[16] for SRS and Minnini et al[17] for SRT. All planning constraints are presented in Table E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.11.408). All plans were normalized to PTV coverage V100% $\geq$95%. Typical isodose lines that correlated to this coverage were 75% to 85%. Target coverage, CI, and DGI were examined to evaluate the treatment plan.

Plan quality evaluation tools

A previously published conformity/gradient index, defined in equations 1 and 2,[10,22,23] was used to define CI and DGI for this study.

$$\boldsymbol{CI} = \frac{\boldsymbol{Prescription\ Volume\ (cc)}}{\boldsymbol{Target\ Volume\ (cc)}} \tag{1}$$

$$\mathrm{DGI} = 100 - \{100 \cdot ((\boldsymbol{Reff}, 50\%\boldsymbol{Rx} - \boldsymbol{Reff}, \boldsymbol{Rx}) - 0.3\,\boldsymbol{cm})\} \tag{2}$$

$$\mathrm{Reff} = \sqrt[3]{\frac{3V}{4\pi}} \tag{3}$$

CI = 1 corresponds to the ideal dose coverage of the target; CI >1 indicates that the irradiated volume exceeds the target volume and covers part of the healthy tissue; and CI <1 indicates that the target volume is not fully radiated. RTOG criteria for CI determine the quality of conformity.[2,24] Due to the emphasis of this study to recommend the DGI guidelines for intracranial SRS/SRT treatments, only plans that were ideal per RTOG 0915[1] and 0813[2] ($1 \leq CI < 1.2$) were considered.

In equation 2, R_{eff} is the effective radius of the Rx isodose volume and $R_{eff,50\%Rx}$ is the effective radius of the isodose line that is equal to one-half of the Rx isodose volume. The effective radius of a volume is the radius of a sphere of equal volume (equation 3).

DGI is a gradient score scaled such that DGI $\geq$100 corresponds to a gradient of 0.3 cm or less. This optimum 0.3 cm gradient was attained empirically from SRS planning cases as a minimum achievable gradient with linear accelerator SRS using noncoplanar arcs and small (<2 cm) circular collimators.[25] DGI scales linearly with the effective radius of the Rx isodose volume. Every additional millmeter in effective radius beyond 0.3 cm volume corresponds to a loss of 10 DGI points. For example, DGI = 100 corresponds to a 0.3 cm effective gradient, DGI = 90 is 0.4 cm effective gradient, DGI = 80 is 0.5 cm effective gradient, and so on. For very small targets (<1 cm), DGI slightly higher than 100 is achievable.

Statistical analysis

A normal continuous probability distribution of DGIs for each group was assumed for statistical analysis. The mean for each size group was chosen to be an ideal DGI. The minimally acceptable DGI criterion was specified to reject the lowest 10% of cases for each group. The inverse cumulative normal distribution function within Microsoft Excel (2016) was used to determine the minimal criteria.

Results and Discussion

Distribution of DGIs with target size

Figure 2 displays the distribution of DGIs for each group, and Table 2 represents the ideal and minimum acceptable guidelines for each tumor size group. From Figure 2 it is evident that DGI values scale linearly with the target size. The data become more scattered with the target size owing to the increase in tumor size range per group.

The effect of target size and shape on DGI

Figure 3a illustrates the distribution of SRS/SRT plans with ideal, minimal, and failed DGI criteria with PTV sizes. The distribution of SRS/SRT plans versus target shape is presented in Figure 1b. Instinctively, DGI is inversely proportional to tumor size. Indeed, the ratio of ideal to minimal to failed DGI decreases with the group size.

Figure 3b shows the distribution of SRS/SRT plans with ideal, minimal, and failed DGI criterion for each target shape group. The plans were divided into 4 groups, representing different target shapes (Fig. 1c). For reasonably homogeneous lesions in the absence of adjacent

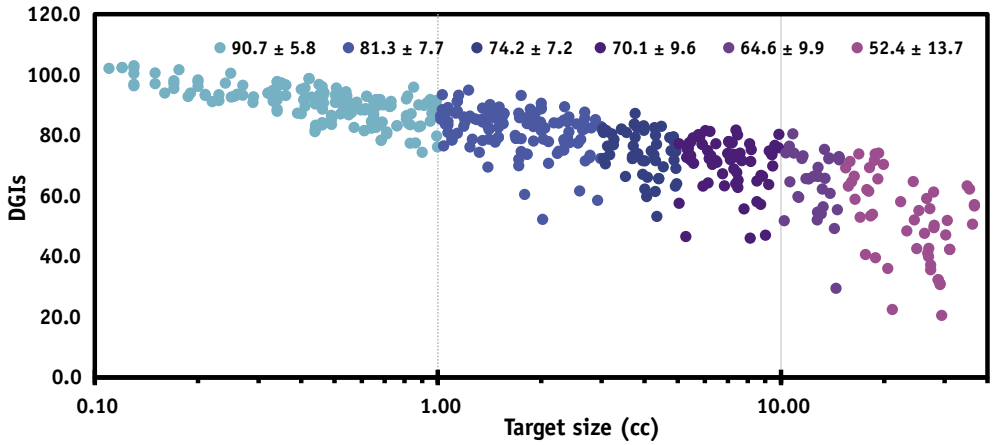

Fig. 2. The distribution of dose gradient indexes (DGIs) with tumor size. Six tumor size groups, Group I (0-1 cm^3), II (1.1-3.0 cm^3), III (3.1-5.0 cm^3), IV (5.1-10.0 cm^3), V (10.1-15.0 cm^3), and VI (15.1-40.0 cm^3), are presented in different colors, with each dot representing the DGI for a single plan within the group. The ideal (average) DGIs with standard deviations for each group are labeled for each group.

radiosensitive structures, the DGI scoring tool is valuable. For circular lesions, 77% of SRS/SRT plans fulfilled the ideal DGI criterion, 19% of plans met the minimal DGI criterion, and only 4% of the SRS/SRT plans failed the DGI criterion.

For lesions adjacent to critical OARs, meeting OAR constraints was a priority over satisfying DGI criteria. Therefore, the percentage of SRS/SRT plans meeting the ideal DGI criterion drops to 55%, whereas the minimum and failed cases rise to 37% and 7%, respectively.

Irregularly shaped lesions located in the absence of adjacent OARs show further weakening of the DGI scores: 46% of SRS/SRT plans achieved the ideal DGI criterion, 41% the minimal DGI, and 13% failed the minimal DGI criteria.

The worst-case scenario for distribution of DGIs is presented in the multilesion group, where only 18% of the plans achieved the ideal DGI criterion, 50% of the plans met the minimal, and 32% of the plans failed the minimal DGI criterion. Many multilesion plans are 2-lesion plans. The DGI is inversely proportional to the distance between the lesions: The more separated the lesions, the easier to meet the DGI guidelines. Also, DGI depends on the number of lesions treated in the same plan, owing to the accumulation of doses from each treatment isocenter. For lesions located in proximity to one another, meeting the ideal or minimal DGI criteria is challenging due to abutting 50% of the Rx isodose lines between lesions. Multilesions plans should be evaluated on an individual basis, and the distance between the lesions and number of lesions need to

Table 2 DGI guidelines for brain lesions in stereotactic radiosurgery/radiation therapy treatments using CyberKnife

Group (tumor volume [cm^3])	Ideal DGI	Minimal DGI
Group I (0-1)	91	83
Group II (1-3)	81	72
Group III (3-5)	74	65
Group IV (5-10)	70	58
Grout V (10-15)	65	52
Group VI (15-40)	52	35

Abbreviation: DGI = dose gradient index.

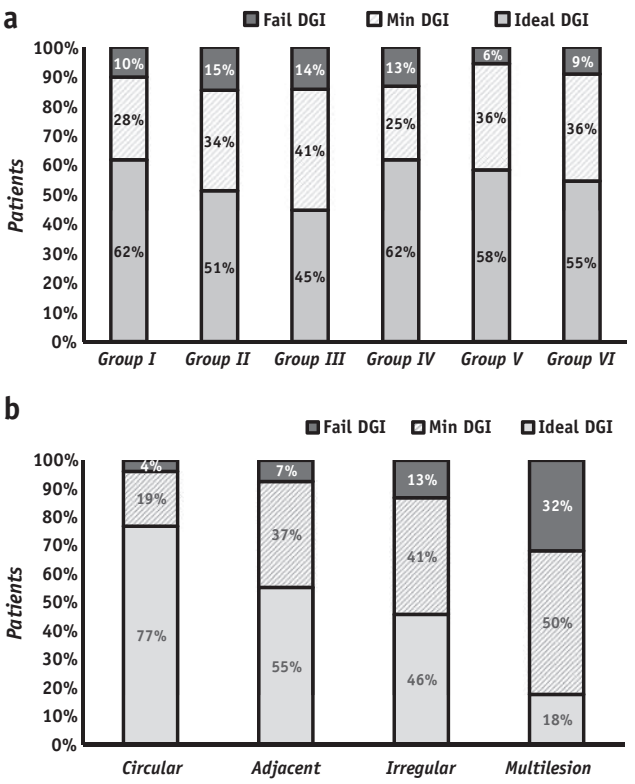

Fig. 3. The distribution of (a) stereotactic radiosurgery/radiation therapy plans with ideal, minimal, and failed DGI criteria with target size; (b) the ideal, minimal, and failed dose gradient index criterion for each target shape group.

be considered during the evaluation of the DGI for SRS/SRT plan.

Effect of DGI on healthy brain volumes (V12Gy for SRS and V24Gy for SRT)

Apart from being dependent on tumor size and shape, DGI also influences the volume of healthy brain tissue receiving radiation dose. Previous studies that examined the value of V12Gy in predicting RN occurring after SRS revealed an increased risk when V12Gy exceeds 10 cm^3,[15] and 7.9 cm^3.[16] A more conservative goal of V12Gy <7 cm^3 was adapted for the evaluation of healthy brain tissue at our institution. Similarly, the hazard of RN was shown to drastically increase for fractionated SRT if the volume of the surrounding healthy brain tissue receiving at least 24 Gy is greater than 16.8 cm^3 (V24Gy >16.8 cm^3).[17] In our study, the mean (median) V12Gy was 3.3 (4.6) cm^3 for 254 SRS treatments and V24Gy was 1.9 (4.1) cm^3 for 241 SRT treatments.

Eighty-one percent of SRS plans passed the criteria for the healthy brain tissue receiving radiation dose V12Gy <7 cm^3. The distribution of normal tissue brain V12Gy is shown in Figure 4a.

Figure 4b presents the distribution of the SRS plans with ideal, minimal, and failed DGIs with V12Gy ≤7 cm^3 (V12Gy Pass) and V12Gy >7 cm^3 (V12Gy Fail). Eighty-seven percent of SRS plans with ideal DGI achieved the V12Gy criterion, whereas this number decreased for plans with minimal (81%) and failed (58%) DGI criteria. Evidently, the plans with higher DGI correspond to the lower V12Gy values.

Regarding SRT plans, only 3% of plans failed the criteria for the healthy brain tissue receiving radiation dose V24Gy <16.8 cm^3. This low number of failures is mainly due to lower mean (median) Rx dose for SRT plans of 2508 (2500) cGy. Therefore, the majority of the plans with ideal DGI, minimal DGI, and failed DGI pass the V24Gy criteria for normal brain tissue.

Figures 4c and 4d present the distributions of V24Gy and SRT plans with ideal, minimal, and failed DGIs with V24Gy ≤16.8 cm^3 (V24Gy Pass) and V24Gy >16.8 cm^3 (V24Gy Fail).

V12 Gy and V24 Gy are influenced by Rx dose, target size, and shape, PTV margin. The effect of these

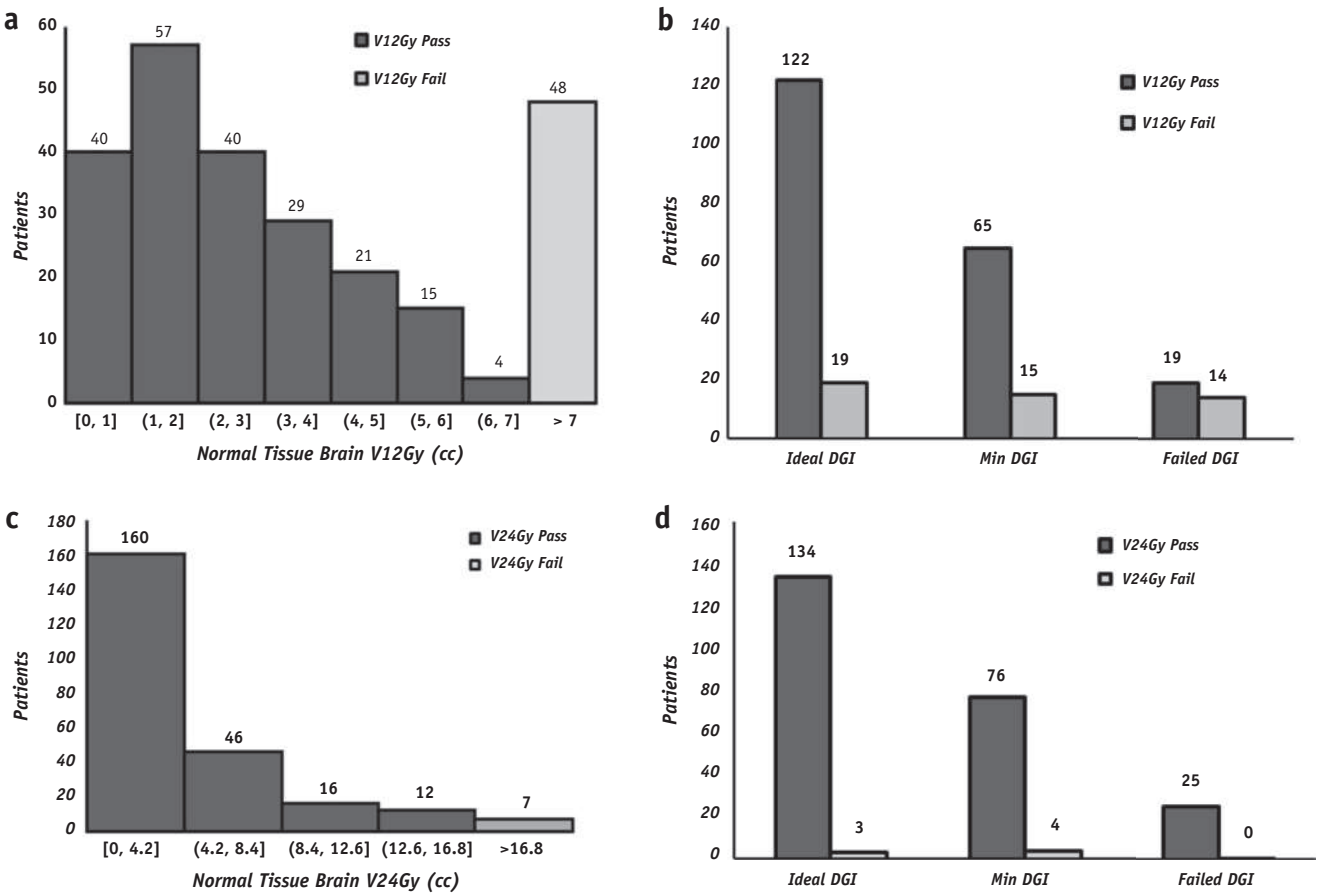

Fig. 4. (a) The distribution of V12 Gy for stereotactic radiosurgery treatments and (b) stereotactic radiosurgery plans with ideal, minimal, and failed dose gradient indexes. (c) The distrubution of V24Gy for stereotactic radiation therapy treatments and (d) stereotactic radiation therapy plans with ideal, minimal, and failed dose gradient indexes.

parameters on V12Gy and V24Gy is investigated and not in the scope of this paper.

Replanning of cases with failed DGIs

To justify minimally acceptable DGI criterion, which rejected the lowest 10% of cases for each group, proposed DGI guidelines were used for replanning of previously failed DGIs plans. Twenty-five percent of failed DGI cases from each target shape group were randomly selected and replanned using DGI guidelines. Of the 15 replanned cases (2 circular, 2 adjacent, 2 irregular, and 9 multilesion), 3 plans fulfilled the ideal DGI score, and the other 12 plans met the minimally acceptable DGI criterion. The differences in the DGIs and V12Gy/V24Gy of initial and replanned plans are presented in Table E2 (available online at https://doi.org/10.1016/j.ijrobp.2019.11.408). By replanning using DGI guidelines, the average DGI score was improved by 5.93 $\pm$ 2.97; V12Gy and V24Gy decreased by 0.67 $\pm$ 0.31 and 0.65 $\pm$ 0.75, respectively. Indeed, replans of adjacent lesions achieved lower doses to critical organs, higher DGIs, and lower V24Gy.

The advantages and disadvantages of DGI

One of the major strengths of this work is that DGIs were evaluated from the actual delivered treatment plans; therefore, the plans were clinically acceptable to practicing physicians. Consequently, no assumptions were made that the plans were "optimal" for any specific case, because treatment plan optimality depends on multiple factors. The other benefit of DGI is that it can be easily calculated by converting the Rx and 50% of Rx isodoses into the volumes and plugging them into a simple formula (equation 2). The price of DGI evaluation simplicity is some limitations in the SRS/SRT quality plan check evaluation. These include lack of consideration of dose homogeneity within the target and radiation doses to any OARs other than nontarget brain tissue. The effect of dosimetric heterogeneity within the target on complication probability remains unclear in the literature.[19] Furthermore, inhomogeneous dose distributions result in higher doses, which will occur within the target and therefore will not lead to increased risk of complication probability.[26] Although there is no direct relation between DGI and the radiation doses to OARs, increasing DGI will ultimately lead to lower nontarget high dose to adjacent organs. Therefore, higher DGI plans may yield lower treatment complications for patients.

Conclusions

Our study proposes DGI guidelines for brain SRS/SRT treatments; a powerful metric in plan quality evaluation. The DGI guidelines enable quantitative evaluation of the dose gradient. Despite certain limitations, our results demonstrate that the DGI, as a complementary tool, provides useful information that cannot be obtained by other indices or display tools.

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