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Original paper

Gamma Knife radiosurgery: Scenarios and support for re-irradiation

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ABSTRACT

Stereotactic radiosurgery (SRS) involves the focal delivery of large, cytotoxic doses of radiation to small targets within the brain, often located in close proximity to radiosensitive normal tissue structures and requiring very low procedural uncertainties to perform safely. Historically, neurosurgeons considered SRS as a one-time, single session procedure. However therapeutic advances and a better understanding of the clinical response to SRS have caused a renewal of interest in a variety of re-irradiation scenarios; including re-irradiation of the same target after prior SRS, SRS treatments after prior broad-field radiation, hypofractionated treatments, and volume-staged treatments. Re-irradiation may in some cases require even greater effort towards minimizing treatment uncertainties as compared to one-time-only treatments. Gamma Knife radiosurgery (GKRS) has evolved over time in ways that directly supports many re-irradiation scenarios while helping to minimize overall procedural uncertainty.

1. Introduction

While stereotactic radiosurgery (SRS) was originally conceived as a single-treatment technique [1], the case for re-irradiation in SRS has grown as a method to manage cases of disease progression after traditional large field treatments [2–4], and local failures [5–9], as well as incomplete response [10]. The high success rates of SRS have also led to attempts to treat larger tumors or tumors very close to sensitive normal tissue structures [11–15].

SRS operates in a regime of exacting constraints with regard to the underlying procedural uncertainties to allow the safe delivery of the required high doses of radiation [16–18]. Re-irradiation potentially further tightens these constraints. This article describes some of the re-irradiation scenarios currently encountered in SRS, followed by a review of the procedural uncertainties involved and how they may be magnified in a re-irradiation scenario. Finally, the article will describe recent technical developments specifically for Gamma Knife radiosurgery (GKRS) and how they help to reduce the procedural uncertainty in ways that support re-irradiation.

2. Re-irradiation scenarios for intracranial radiosurgery

We will use a working definition of re-irradiation as any radiation treatment (SRS or otherwise) delivered subsequently to an initial radiation treatment. Based on this expansive definition, there are a number of re-irradiation scenarios one could envision for SRS. Table 1 provides a summary of some of the larger studies involving GKRS re-irradiation scenarios, some of which are described in more detail below.

2.1. Re-irradiation of the same treatment site

The scenario which is most straightforwardly a re-irradiation scenario is an additional SRS procedure to a site which was previously treated with SRS to salvage cases which failed or had an incomplete response. One of the earliest reports establishing the safety of tumor re-irradiation at the same site was by Bhatnagar et al. [2], which examined 26 patients including both benign and malignant tumors, finding a decrease in steroid use (as a surrogate for quality of life) and minimal neurocognitive decline. A number of centers have subsequently reported on repeat GKRS for locally recurrent brain metastases [7–9], benign tumors [21,23–26,29,30], and functional indications [19,20,27,31,32]. Fig. 1 shows an example of a trigeminal neuralgia case being retreated after a local failure. An important concern for re-irradiation of the same treatment site is the risk of adverse radiation effects such as radiation necrosis, with the above studies reporting a frequency 9% to 29% at 1 year [7–9].

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Table 1
Summary of clinical GKRS studies involving re-irradiation scenarios [2,7,23–28,8,9,12,13,19–22]. The number of patients treated in a re-irradiation scenario is reported, as well as the total number of patients treated for that indication if reported.

Year	Author(s)	Journal	Clinical setting	# re-irradiation patients in study/total treated (if reported)
2002	A. Bhatnagar, et al.	IJROBP	Re-irradiation for primary and metastatic tumors	26/3443
2008	S. Yomo, et al.	Neurosurgery	Re-irradiation for vestibular schwannoma	15/1951
2012	K. Park, et al.	Neurosurgery	Re-irradiation for trigeminal neuralgia	119
2012	A. Wojcieszynski, et al.	J. Clinical Neuroscience	Re-irradiation for recurrent meningioma	19/651
2012	H. Kano	Progress in Neurological Surgery	Volume-staged radiation for AVMs	47
2014	C. Tuleasca, et al.	J. Neurosurgery	Re-irradiation for trigeminal neuralgia	13/737
2015	C. Helis, et al.	Neurosurgery	Re-irradiation for trigeminal neuralgia	152
2015	S. Lonneville, et al.	Surg Neurol Int	Re-irradiation for vestibular schwannoma	25
2017	W. McKay, et al.	J. Neurosurgery	Re-irradiation for locally recurrent brain metastases	32
2017	P. Koffer, et al.	World Neurosurgery	Re-irradiation for locally recurrent brain metastases	22
2017	R. Kotecha et al.	Neurosurgery	Re-irradiation for SRS for multiply recurrent brain metastases	59
2017	A. Ilyas, et al.	J. Clinical Neuroscience	Volume-staged radiation for AVMs	12
2017	B. Pollock	Clinical Neurosurgery	Volume-staged radiation for AVMs	34
2018	P. Balermpas, et al	PloS One	Re-irradiation for locally recurrent brain metastases	31
2018	G. Mehta, et al.	J. Neurooncology	Multicenter repeat SRS for Cushing's	20
2018	A. Lin, et al.	IJROBP	Re-irradiation for recurrent meningioma	43/662

A

B

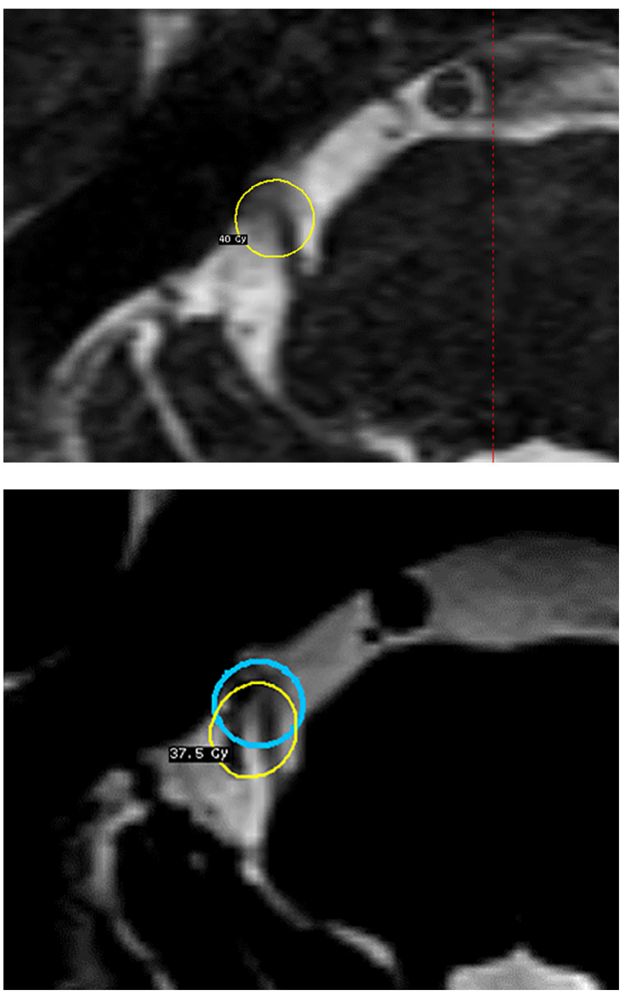


Fig. 1. Example GKRS treatment plans of a re-irradiation for trigeminal neuralgia. 1a) T2 SPACE MR and treatment plan for the first GKRS of the right trigeminal nerve. 40 Gy prescription isodose (yellow line) shown targeting the nerve. 1b) Treatment plan for the repeat GKRS treatment. Thicker blue line is the prescription isodose line from the first treatment. The yellow line is the 37.5 Gy prescription isodose for the repeat treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. SRS re-irradiation after partial-brain or whole-brain irradiation

Another common re-irradiation scenario is one in which a patient had a previous traditionally fractionated radiation procedure, whether whole-brain radiotherapy (WBRT) or partial-brain radiotherapy (PBRT). GKRS may occur near-concurrently to the primary treatment as in the case of a radiosurgical boost to one or more targets [33–36], or it may be a later SRS procedure to deal with local or distal failures after the primary radiation treatment [37,38]. The decision as to whether to treat with upfront SRS and delay WBRT or to use SRS as salvage after WBRT is an open question. Studies have shown that the dose to the whole brain delivered during SRS for multiple brain metastases does not depend on the number of lesions treated, but rather the total volume of lesions treated. This may mean that treated with SRS upfront may help delay significant dose to the whole brain until such time WBRT is necessary [39].

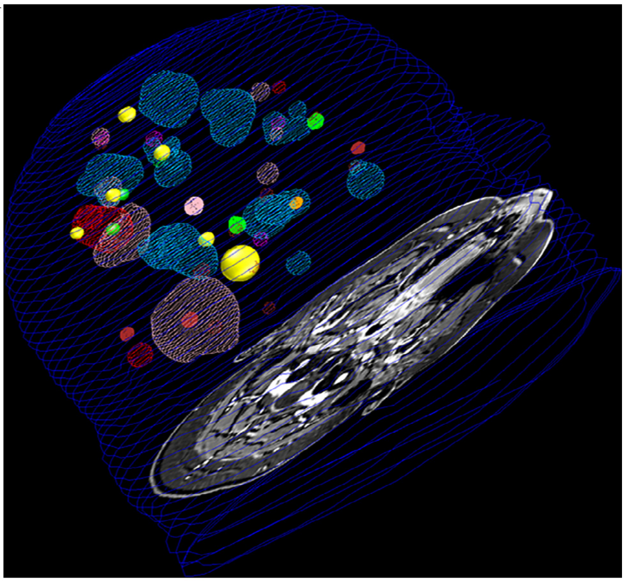
2.3. Repeat radiosurgery for new tumors

As SRS is by design a focal treatment, there is always a possibility for the development of new tumors in metastatic cases [40], and out-of-field failures for gliomas and other primary malignant brain tumors [41]. In many of these cases, patients have either already been treated with WBRT (as well as SRS) or WBRT is being deferred for as long as possible. In some cases patients can be managed for an extended period of time by this strategy, with repeated SRS utilized when new tumors appear, and such an approach can convey a high likelihood of local control [5,22,42]. Fig. 2 demonstrates the cumulative treatment plan for a patient treated with GKRS for a total of fifty-five individual tumors over nine GKRS sessions (in addition to a course of whole-brain radiotherapy) over a period of thirty-five months.

2.4. "Volume-staged" radiosurgery

Radiosurgery is premised on the idea of the dose-volume relationship; i.e. high, cytotoxic doses to a target are possible as long as the target is small to moderate in size. As the target volume increases, the risk of radiation-induced toxicity and complication proportionally increases as well. Pathologies such as large arteriovenous malformations may be surgically unresectable, may be not amenable to embolization, and may be too large for traditional single-fraction SRS. One such technique that has recent gained in popularity in these cases is a "volume-staged" SRS technique, where the AVM nidus is divided at time of treatment planning into two or more nidal sub-volumes. Each sub-

A



B

# months post initial GKRS	# tumors treated	Vol 12Gy (cc)	Skull mean(SD) dose (Gy)
7/2013	1	0.6	0.1 (0.3)
+3 months	5	3.4	0.4 (0.8)
+7 months	5	15.9	0.9 (1.7)
+10 months	11	5.1	0.6 (0.9)
+23 months	8	43.8	1.4 (2.3)
+24 months	4	2.0	0.2 (0.5)
+27 months	6	14.6	0.6 (1.4)
+31 months	9	46.2	1.6 (2.3)
+34 months	6	6.2	0.4 (0.9)
+15 months - WBRT (30 Gy in 10 fractions)			

Fig. 2. Cumulative GKRS treatment for 55 metastatic lesions in 9 GKRS treatments over a period of 34 month in one patient. 2a) 3D view of the prescription isodose volumes for each plan, color coded by treatment. 2b) Treatment statistics for each treatment, color coded to match the 3D view in 2a.

volume is treated to a large (even standard) single-fraction radiosurgery treatment, usually separated in time by months. Volume staging techniques have been reported with promising results in the literature [12–14,28]. Fig. 3 illustrates a large AVM treated with volume-staged GKRS, along with the resolution of the AVM on follow-up imaging.

2.5. Fractionated or multi-session radiosurgery

Finally, SRS may be delivered in more than a single fraction. Historically this has been impractical, primarily because of the use of external stereotactic frames. However as described in more detail below, with the advent of onboard image-guidance, thermoplastic mask immobilization, and intrafraction motion management, multiple-fraction SRS is now a practical alternative for clinical situations requiring extra protection for nearby critical structures, larger lesions, or when there may be some radiobiological advantage to fractionation [11,43–45]. In North America, hypofractionated SRS schedules are commonly two to five daily fractions, however some centers are investigating a split-treatment technique where a tumor is treated in two fractions of 15 Gy, separated by approximately one month [46].

3. What makes re-irradiation difficult

SRS operates under an extremely critical set of constraints. The delivery of high-radiation doses conformally to targets requires carefully shaped radiation fields with extremely sharp dose falloff outside of the target. Targets are frequently close to critical normal tissue structures that are frequently sensitive to radiation. Achieving these constraints in a re-irradiation setting becomes more difficult as a clinically useful system must be able to maintain low procedural uncertainty while providing for a practical multi-session workflow and an ability to keep records of each patient's progress over a variety of treatment scenarios.

3.1. The need for low procedural uncertainty in re-irradiation

Several studies have demonstrated the effects that can occur if the uncertainty levels of SRS are relaxed. Treuer et al. [47] reported on a simulation of the effects of a geometric miss on the predicted tumor control probability for metastases and the predicted occlusion probability for AVMs. In both cases, a geometric miss of approximately 1.3 mm leads to a 5% reduction in the probability of a successful treatment. However a geometric miss does not only affect the intended target. Kim et al. [48] reported on a similar study that demonstrates that a geometric miss to targets nearby critical structures may result in higher-than planned doses to those critical structures. Finally, smaller tumors are more sensitive to dosimetric errors as targeting errors increase [49].

SRS is a multi-step technique with an interrelated chain of sources of uncertainty which must be understood and minimized to prevent the unwanted outcomes described above. An in-depth discussion of each is beyond the scope of this paper, however a high-level list would include categories of uncertainty such as device mechanics, dosimetric calibration, stereotactic coordinate system definition, patient immobilization within the coordinate system, imaging geometry, target visualization, target definition, target localization, treatment planning dosimetric calculation, and radiobiological response [16]. Uncertainties can be modelled as having a random component and a systematic component, where the random component results in a blurring of a delivered dose due to day-to-day variation, and a systematic component that results in an offset of the delivered dose. In a single-fraction treatment such as SRS the entirety of the uncertainty is systematic. The significance of the random component of uncertainty increases with the number of treatment sessions for a given target, however the random component usually has less significance than the systematic component [50].

These sources of uncertainty are not unique to GKSRS, but the dosimetric constraints on any SRS technique means that the options to compensate for uncertainty are limited. Conventional radiotherapy has evolved a formal convention of treatment margins to compensate for different sources of procedural uncertainty [51–53]. Various expansions of the intended target tissue volume ensures that targeted areas of tissue will receive an adequate dose of radiation even under assumed uncertainties. Similar expansions of organs at risk (OARs) ensure that radiosensitive structures will be spared. Formal algorithms such as the widely-cited Van Herk margin formula [54] can be used to determine appropriate treatment margins for conventional radiotherapy, but are not as applicable to SRS scenarios where the number of treatment fractions is low [55].

The effect of re-irradiation on treatment uncertainties likely varies depending on the specific treatment situation and the specific source of uncertainty. However in general, re-irradiation will cause an increase in random uncertainty Thus, for a fixed total acceptable uncertainty, re-irradiation scenarios may require an even lower systematic uncertainty than for one-time SRS procedures. Minimizing systematic uncertainty through device and procedure design in effect leaves more room for re-irradiation to safely be considered.

3.2. The need for practical multi-session workflows

Another challenge for re-irradiation in SRS is that the work involved must be practical and acceptable to patients, including the wok

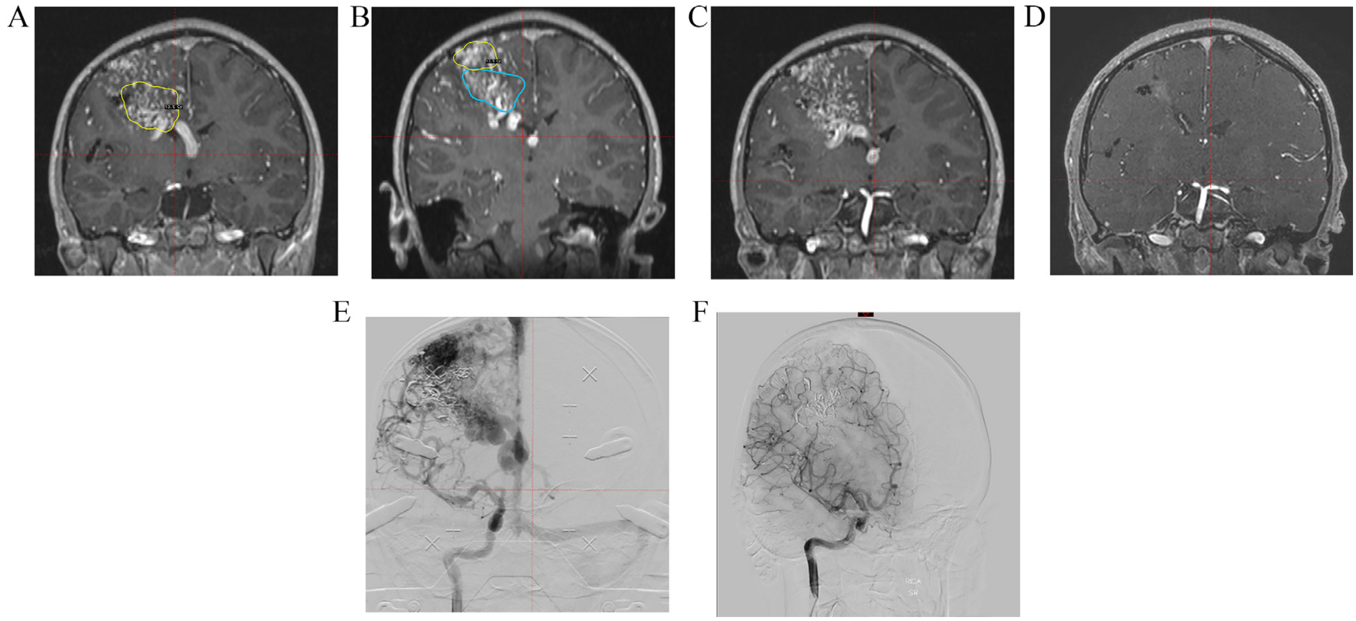


Fig. 3. Example of GKRS using a "volume-staged" technique. 3a) MRI of a large right frontal AVM and the prescription isodose line for the first stage GKRS. Rx = 13.5 Gy- > 50% isodose; $V_{13.5Gy}$ = 14.6 cm^3; V_{12Gy} = 17.1 cm. 3b) MRI and prescription isodose line for the second stage GKRS, ~1 month after the first stage. Rx = 13.5 Gy- > 50% isodose; $V_{13.5Gy}$ = 8.9 cm^{3s}; $V_{12\ Gy}$ = 10.8 cm^3. 3c,f): The MRI (3c) and angiography (3e) of the AVM at the time of the first GKRS treatment. 3d,f) The MRI (3d) and angiography (3f) of the AVM showing confirmation of AVM obliteration. Note on abbreviations: Rx = prescription isodose, V_{xxGy} = volume of tissue receiving > = xx Gy absorbed dose.

required to setup and immobilize the patient in the correct treatment position. SRS traditionally makes use of a stereotactic frame fixed to the outer table of the skull via fixation pins which serves to both immobilize the patient for treatment as well as defines a targeting coordinate system. In single-session treatments this remains an attractive option. However in settings where patients may be re-irradiated multiple times in close succession, placing and removing frames may be impractical.

There have been several attempts in the past to treat patients with SRS over multiple days, including by leaving them in stereotactic frames for multiple days and treating one fraction each day [56], and devising frames that can be manually removed and replaced on a fixed set of pins [57]. A variety of relocatable frame systems have been developed with a range of acceptance in clinical practice including thermoplastic masks [58], dental-fixation based frames [59,60], combination techniques [61], and relocatable frames with auxiliary monitoring via optical tracking [62] or vacuum monitoring [63]. These can achieve magnitudes of setup uncertainty similar to traditional stereotactic frames using onboard image guidance, but require intrafraction motion management solutions to compensate for their less rigid immobilization [64,65].

3.3. The need for longitudinal tracking of patients

The variety of re-irradiation situations that may occur in SRS can make longitudinally tracking a given patient's treatments complicated. Clear data is required to ensure the correct targets are being treated (or re-treated), and that the correct dose is being delivered to each target. Conventional fractionated radiotherapy partially address this problem through the creation of "record and verify" systems, which track treatment fields as they are delivered and ensure (amongst many features) that the correct fields are delivered the intended number of fractions [66]. Some treatment planning systems (and independent software systems) can create composite doses over many treatment courses through time, and some can apply radiobiological models [67] to account for the effects of dose/fractionation and time.

4. Gamma Knife support for re-irradiation scenarios

Gamma Knife support for re-irradiation scenarios falls under three general categories of features: Minimizing beam delivery uncertainty, providing practical multi-session workflows, and assisting with longitudinal data management tasks over multiple irradiations. The net result is a system that can accommodate techniques ranging from traditional single-fraction treatments and traditional hyper-fractionated techniques, to combination techniques that treat some tumors under different fractionation regimes.

4.1. Minimizing beam delivery uncertainty

The GKRS platform inherently supports re-irradiation scenarios through a system design that places emphasis on low uncertainty of the beam delivery and mechanical components of the system.

The Gamma Knife system is well known for its cobalt-60 (^{60}Co) based source of radiation. ^{60}Co has a benefit of low uncertainty with respect to beam delivery as the photon energy, the activity of each ^{60}Co source at time of manufacture, and the decay of the sources with time are well known, so ultimately the effective dose rate of the machine is predictable. The primary collimator inside the Perfexion and Icon models designed so the 192 individual beams converge to within a 0.5 mm diameter sphere [68], maintaining low uncertainty in the geometry of the radiological focus.

The Perfexion and Icon Gamma Knife models position the patient within the targeting coordinate system by moving the patient bed (more officially known as the Patient Positioning System, or PPS). The only other significant moving parts are the eight source sectors, which position each set of 24 sources over the requested beam channel size for each isocenter in the treatment plan. The mechanical design and control system of the Perfexion and Icon models use linear encoders to monitor absolute position and rotational encoders to guide PPS and sector motion. In the case of PPS motion, the control system will safely terminate a treatment if the absolute position deviates radially from the requested location by greater than 0.2 mm.

The coincidence between the radiological focus point (RFP) and the position of the PPS at the requested stereotactic coordinate is maintained by a multi-level calibration scheme similar to the calibration chain from Primary Standards Dosimetry Laboratories (PDSLs) to Secondary Standards Laboratories (SSDLs) to the clinic used in the wider medical physics community for calibration equipment [69]. A set of master diode tools maintained by the manufacture are calibrated against a well-characterized "reference" Gamma Knife. These master tools are then used to determine the calibration offsets of a given Gamma Knife unit. A clinical diode tool maintained at each site is then calibrated against one of these master diode tools [70]. During semi-annual manufacturer maintenance a quality assurance (QA) test is performed using a master tool to ensure the coincidence between the RFP and the PPS is < 0.15 mm radially for at a centered position with a 4 mm isocenter. Monthly QA using the clinical diode tool is used by the onsite physicist to ensure the constancy of coincidence remains < 0.3 mm radial [71].

For traditional single-session GKRS a stereotactic frame serves the dual role of immobilizing the patient during the procedure and defining the location of the stereotactic coordinate system relative to the patient's anatomy. The frame system is generally assumed to have low mechanical uncertainty. One study examining the frame system performance with cone-beam computed tomography (CBCT) imaging found a setup uncertainty of 0.40 (0.66) mm and an intrafraction immobilization uncertainty of 0.05 (0.22) mm [mean(SD)][72]. However, there is some evidence that the immobilization uncertainty is somewhat dependent on the length of fixation pin used and the load placed on the pins by the weight of the patient's head [73].

4.2. *Gamma Knife support for practical multiple session treatments*

4.2.1. *Support for multiple session treatments in GKRS: the extend system*

The multiple-fraction treatments solution for GKRS using the Perfexion model is through the use of a vacuum-assisted, dental-impression guided relocatable frame system known as the Extend system [63,74]. The system made use of a measurement template and digital linear measurement probes to record the position of the patient at the time of treatment simulation, and are used again to assist in re-positioning the patient for treatment in the same position. Several studies reported residual setup uncertainties using the system to be sub-millimetric [63,75,76] with diligent use of the system.

4.2.2. *Support for multiple session treatments in GKRS: the icon system*

On the Icon model, integration of image-guidance and motion tracking technologies created opportunities for new designs that could better support multiple-fraction situations. The Icon system uses an onboard cone-beam-computed-tomography (CBCT) system [72] to provide images of the patient in treatment position in stereotactic space. An intrafraction motion management system makes possible real-time tracking of the patient's head position, with gating of the treatment if the patient moves out of the required treatment position. These combined capabilities make possible treatments without a frame system, using only a thermoplastic mask system for immobilization [77].

4.2.2.1. *Patient-specific immobilization.* Patient immobilization on the Gamma Knife Icon system is comprised of a customized thermoplastic mask system combined with a moldable, patient-specific head cushion and patient head-support system which accepts the head-cushion and has a snap-in mount for the thermoplastic mask.

The combination of the patient-specific cushion and thermoplastic mask serve as a guide for patient setup on the machine, and also act to immobilize the patient's head during treatments. Various studies have been performed on the performance of thermoplastic mask systems, [43,44,78]. Uncorrected motion within thermoplastic masks have been found to be greater than 2.0 mm [79] and immobilization performance of masks may deteriorate with time [80]. For this reason, intrafraction motion management and treatment gating are used with the Icon system and are detailed below.

4.2.2.2. *CBCT-based positioning.* The Icon system uses an onboard cone-beam computed tomography (CBCT) system for determining the current patient position just before treatment and correcting the treatment plan for the difference in position relative to the patient position (also determined via onboard CBCT) at the time of treatment planning. The CBCT system has a known calibration offset to the RFP of the treatment machine, determined using an imaging quality assurance (QA) tool containing six ball-bearings at known stereotactic coordinates, and maintained by the manufacturer. A similar QA tool maintained in the clinic including four known-coordinate ball-bearing imaging targets is used to verify the accuracy of localization, with a maximum acceptable radial error of 0.4 mm. Studies have found the system to be quite stable over time, with one study reporting the results of 30 days of QA tests to have a mean (SD) maximum deviation of 0.13(0.05)mm, and a maximum reported deviation of 0.22 mm [81].

4.2.2.3. *Intrafraction motion management.* The intrafraction uncertainty of a thermoplastic mask-based immobilization system is likely too large for safe use in a radiosurgery settings by itself. For this reason, a motion tracking system, named the High-Definition Motion Management (HDMM) system, based on infrared markers and a stereoscopic infrared camera system is used on the Gamma Knife Icon system to track patient motion and gate the treatment if the patient should deviate from the intended position beyond an acceptable threshold. If the patient quickly returns to a position below the threshold, treatment resumes. If the patient does not return to an acceptable position, the system will pause the treatment, and a new CBCT can be obtained to re-establish the patient's reference position.

A study performed on the performance of the HDMM system demonstrates that the nose marker is a suitable surrogate for motion of an intracranial target, with the marker displacement on average approximately twice that of the actual displacement of target anatomy in phantom studies [64].

4.3. *Gamma Knife support for longitudinal data management*

The clinical requirement to re-irradiate patients requires careful dose accounting. Methods are needed to track which targets have been previously treated and on which treatment session(s). Dose accumulation is helpful to understand the cumulative absorbed dose received by targets, normal tissue structures, and the brain as a whole. In support of the large variety of re-irradiation permutations, the Gamma Knife treatment planning system tracks the number of planned fractions as well as each partially or completely completed fraction. Absorbed doses from completed fractions vs total planned fractions may be displayed and compared. Changes to the number of targets or dose/fractionation can be implemented and the updated cumulative absorbed dose displayed. Fig. 4 shows an example of dose accumulation, allowing the dosimetrist to view the absorbed dose contributed by the currently planned treatment course, or the combined dose from prior treatments. It should be noted that while the current version of the treatment planning system can accumulate absorbed dose, it does not attempt to apply any radiobiological models to predict the biological effect of re-irradiation.

5. Conclusion

As SRS continues to broaden its role in neurosurgical care it is increasingly likely that patients will be managed through a combination of techniques and may undergo multiple SRS procedures over time including a variety of re-irradiation scenarios. The current Gamma Knife models allow flexibility in treatment approaches that permit the possibility for re-irradiation when clinically indicated. The evolution of

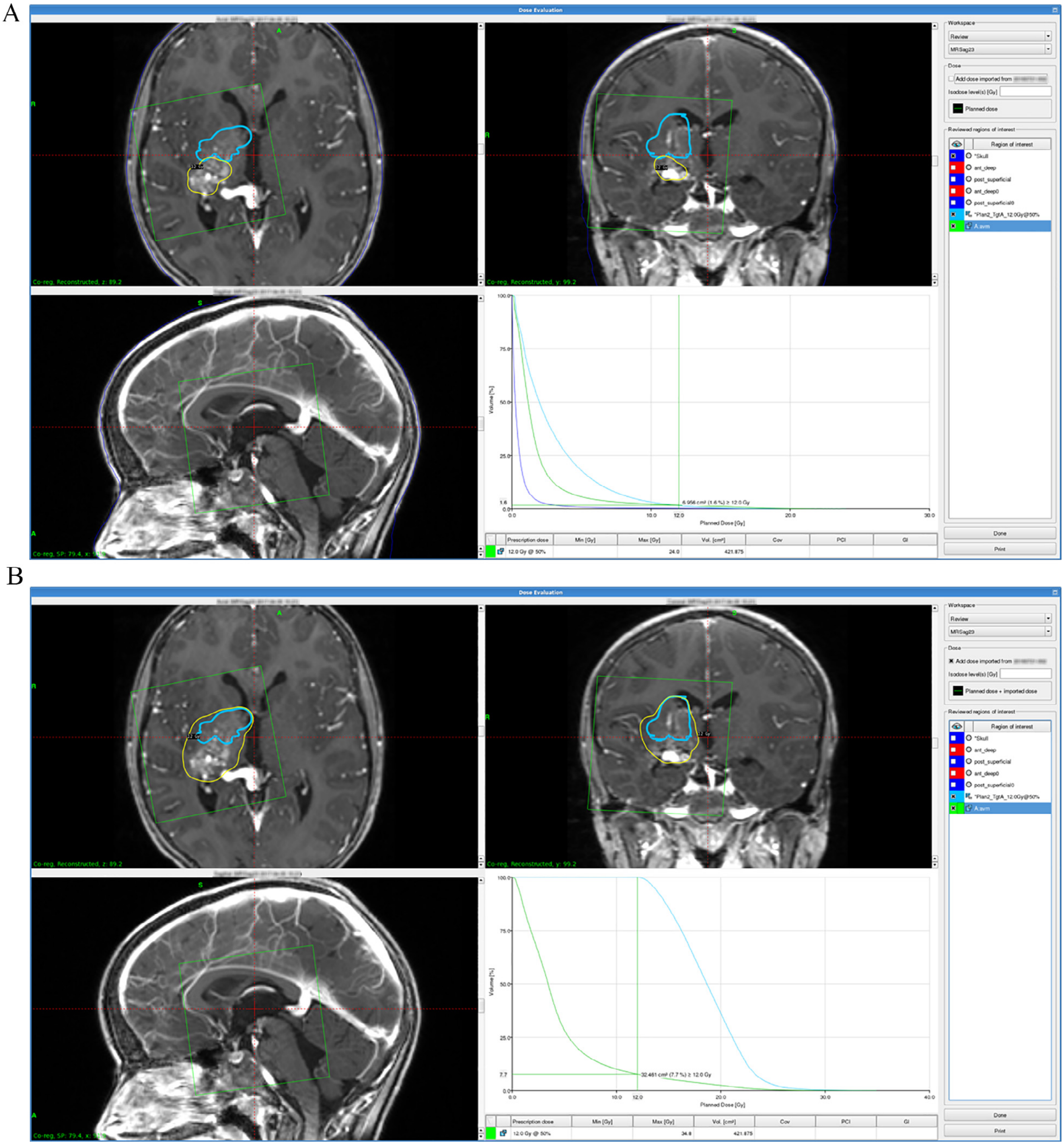


Fig. 4. Gamma Knife treatment planning support for dose accumulation. 4a) View of the second GKRS for a volume-staged AVM showing the dose contribution and dose-volume histograms for the second GKRS only. 4b) View of the second GKRS showing the combined dose contribution from both the first and second GKRS sessions.

the Gamma Knife system has made it possible to serially track treatment plans for patients undergoing multiple single-fraction procedures, create multiple-session treatments using a bite-block assisted, relocatable frame system, and develop capability to fully manage re-irradiation scenarios using onboard-image guidance and intrafraction motion-management systems as realized by the Gamma Knife Icon platform. Critically, this evolution maintains a low treatment delivery uncertainty, maintaining a safety margin helpful to re-irradiation situations.

However, much work remains to better understand the radiobiological implications of various re-irradiation scenarios and to include this understanding in a way that reduces the radiobiological components of treatment uncertainty. Improvements in treatment planning automation and treatment re-planning will continue to refine and improve workflows for multiple-fraction and re-irradiation treatments for patients, increasing convenience and improving treatment efficacy.

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