Conventionally fully fractionated Gamma Knife Icon re-irradiation of primary recurrent intracranial tumors: the first report indicating feasibility and safety

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OBJECTIVE With the incorporation of real-time image guidance on the Gamma Knife system allowing for mask-based immobilization (Gamma Knife Icon [GKI]), conventionally fully fractionated (1.8–3.0 Gy/day) GKI radiation can now be delivered to take advantage of an inherently minimal margin for delivery uncertainty, sharp dose falloff, and inhomogeneous dose distribution. This case series details the authors’ preliminary experience in re-irradiating 7 complex primary intracranial tumors, which were considered to have been previously maximally radiated and situated adjacent to critical organs at risk.

METHODS The authors retrospectively reviewed all patients who received fractionated re-irradiation using GKI at the Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada, between 2016 and 2021. Patients with brain metastases, and those who received radiotherapy courses in 5 or fewer fractions, were excluded. All radiotherapy doses were converted to the equivalent total dose in 2-Gy fractions (EQD2), with the assumption of an α/β ratio of 2 for late normal tissue toxicity and 10 for the tumor.

RESULTS A total of 7 patients were included in this case series. Three patients had recurrent meningiomas, as well as 1 patient each with ependymoma, intracranial sarcoma, pituitary macroadenoma, and papillary pineal tumor. Six patients had undergone prior linear accelerator–based conventional fractionated radiotherapy and 1 patient had undergone prior proton therapy. Patients were re-irradiated with a median (range) total dose of 50.4 (30–63.4) Gy delivered in a median (range) of 28 (10–38) fractions with GKI. The median (range) target volume was 6.58 (0.2–46.3) cm³. The median (range) cumulative mean EQD2 administered to the tumor was 121.1 (107.9–181.3) Gy, and the median (range) maximum point EQD2 administered to the brainstem, optic nerves, and optic chiasm were 91.6 (74.0–111.5) Gy, 58.9 (6.3–102.9) Gy, and 59.9 (36.7–127.3) Gy, respectively. At a median (range) follow-up of 15 (6–42) months, 6 of 7 patients were alive with 4 having locally controlled disease. Only 3 patients experienced treatment-related toxicities, which were self-limited.

CONCLUSIONS Fractionated radiotherapy using GKI may be a safe and effective method for the re-irradiation of complex progressive primary intracranial tumors, where the aim is to minimize the potential for serious late effects.

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KEYWORDS Gamma Knife Icon; re-irradiation; fractionated radiotherapy; oncology; stereotactic radiosurgery; tumor

The Leksell Gamma Knife (GK) (Elekta AB), initially developed at the Karolinska Institute in 1968, is a dedicated specialized treatment unit for the administration of stereotactic radiosurgery (SRS) to intracranial lesions.1 The GK Perfexion is the most recent iteration, incorporating a single tungsten collimator with an 8-sector design. However, it is still based on patient immobilization with an invasive frame, which has been associated with patient anxiety and pain in a significant proportion of patients.2 Furthermore, treatment times are lengthier than those with traditional linear accelerator (LINAC)–based therapy and several hours is needed depending on the
source strength. Together, these limitations have prevented the delivery of fractionated GK radiation.

In 2015, GK was fitted with an on-board cone-beam CT and a reflective infrared motion management system to allow for treatment gating and compensation of head movement. This permitted the frame to be replaced with a thermoplastic mask-based head immobilization system, and this newly updated Gamma Knife Icon (GKI) represents frameless GK treatment. Despite the absence of a frame, GKI retains significant precision and, according to the findings of comprehensive motion analyses, our approach is to apply a small planning target volume (PTV) margin of 1 mm craniocaudally and 0.5 mm radially.

With the ability to deliver conventionally fractionated GKI treatments, we applied this technology to challenging primary tumors that had been considered maximally radiated and were not candidates for a salvage short course of hypofractionated SRS (HSRS). The fully fractionated re-irradiation approach of delivering 1.8–3.0 Gy/day was selected owing to extent/volume of disease and proximity to organs at risk (OARs), as well as to reduce the potential for both acute and late adverse effects including radiation necrosis. Furthermore, GKI was selected, as opposed to delivery with a LINAC-based system, to take advantage of the inherent inhomogeneity of the dose distribution and associated escalation of the mean dose by prescribing to a low isodose line, sharp dose falloff, lower dose rate, and limited PTV margin.

We hypothesized that GKI-based re-irradiation is feasible and results in acceptable rates of toxicity and tumor control for patients with otherwise no reasonable means for further definitive oncological curative therapy. The objective of this report was to provide the first clinical outcomes of our institutional series.

Methods

We retrospectively identified all patients with primary intracranial tumors treated by using fractionated re-irradiation and GKI at our institution from 2016, when it was first commissioned, to December 2021. Patients with brain metastases, or those who received HSRS in 5 or fewer fractions, were excluded from the current study. Baseline characteristics, treatment outcomes, and prior radiotherapy details are summarized, and GKI treatment-planning details and metrics were obtained from the Leksell GammaPlan treatment-planning system (Elekta Instrument AB). The primary outcome was toxicity, and the secondary outcome was tumor control.

The maximal doses to the targets and OARs were converted to the equivalent total dose in 2-Gy fractions (EQD2) with the following formula: EQD2 = D[(d + α/β)/[2 + α/β]], where D represents the total dose, d represents the dose per fraction, α represents the linear (first-order dose-dependent) component of cell killing, and β represents the quadratic (second-order dose-dependent) component of cell killing. Recurrent tumor was assumed to have an α/β ratio of 10 Gy, and normal tissues an α/β ratio of 2 Gy for late effects.

Patients were in the supine position, and their heads were immobilized in the thermoplastic mask specific to the GKI unit. Axial, volumetric, 1.5-mm-thick MR images, including both T1-weighted post-gadolinium and T2-weighted FLAIR sequences, were fused with the planning cone-beam CT scan. Additionally, contrast-enhanced CT scans and T2-weighted high-resolution sequences (with and without fat saturation) were obtained and fused for evaluation of skull-based tumors. The gross tumor volume was contoured using a combination of all acquired planning sequences. A 0.5-mm radial margin and 1-mm craniocaudal margin was applied to generate a PTV, as per our internally validated institutional protocol. All treatment planning was performed using Leksell Gamma Plan (Elekta AB). All patients were followed with a volumetric MR brain scan every 3–4 months in conjunction with a clinical assessment.

Results

A total of 7 patients met our inclusion criteria (Table 1). Three patients had recurrent meningioma, 1 high grade sarcoma, 1 pituitary macroadenoma, 1 ependymoma, and 1 papillary pineal tumor. The median (interquartile range [IQR]; range) age at re-irradiation was 59 (29; 31–66) years, and the median follow-up duration after GKI re-irradiation was 15 (12; 10–42) months.

The median (IQR; range) time between radiotherapy courses was 88 (84; 16–206) months. The median (IQR) total dose and number of fractions of prior radiotherapy were 50 (5) Gy and 30 (2.5) fractions, respectively. The median (IQR; range) total dose and number of fractions with re-irradiation GKI were 50.4 (2.7; 30–63.4) Gy and 28 (1.5; 10–38), respectively, with median (IQR; range) target maximum EQD2 (Dmax) and mean EQD2 (Dmean) of 96.9 (16.66; 71.9–149.4) Gy and 68.7 (9.2; 45.5–108.6) Gy, respectively. The median (IQR; range) cumulative EQD2 of the mean tumor dose, accounting for both primary and re-irradiation courses, was 121.1 (9.58; 107.9–181.3) Gy. Dosimetric details are summarized in Table 2, and data for the OARs are summarized in Table 3.

Case 1

An adult patient presented with right-sided oculomotor nerve palsy and had a 3.6-cm extra-axial lesion in the right middle cranial fossa invading the cavernous sinus.

The patient underwent craniotomy and subtotal resection, with pathological analysis revealing WHO grade II meningioma. Given the residual disease, he underwent fractionated radiotherapy with 54 Gy/30 fractions with LINAC-based intensity-modulated radiotherapy (IMRT) administered to the tumor and surgical bed, with a 10 Gy/5-fraction boost administered to the GKI (total exposure 64 Gy/35 fractions).

The patient began experiencing worsening facial numbness 1 year later, and follow-up MRI showed progression of the lesion. Despite re-resection, subsequent imaging showed serial growth of recurrent disease measuring 1.3 cm. Given that the previously administered maximum doses to the brainstem, optic chiasm, and optic nerve all approached the limit of 54 Gy and the short relative time period from prior radiation exposure (16 months), the decision was made to re-irradiate with GKI and 30 Gy/10
**TABLE 1. Patient and previous treatment characteristics**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Anatomical Location</th>
<th>Dose (Gy)/Fractions (no.)</th>
<th>Time From RT to GKI Course (mos)</th>
<th>Follow-Up After GKI (mos)</th>
<th>Toxicity Outcomes</th>
<th>Oncological Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Grade II meningioma</td>
<td>Rt cavernous sinus/sphenoid wing</td>
<td>54/30 + 10/5 GKI boost</td>
<td>30/10</td>
<td>16</td>
<td>13</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Papillary pineal tumor</td>
<td>Pineal</td>
<td>54/30</td>
<td>50.4/28</td>
<td>42</td>
<td>22</td>
<td>Fatigue/tiredness</td>
</tr>
<tr>
<td>3</td>
<td>Grade II meningioma</td>
<td>Frontal parasagittal</td>
<td>54/30</td>
<td>50.4/28</td>
<td>93</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Grade II ependymoma</td>
<td>Posterior fossa/brainstem</td>
<td>54/30</td>
<td>45/25</td>
<td>88</td>
<td>42</td>
<td>Headache &amp; ataxia</td>
</tr>
<tr>
<td>5†</td>
<td>High-grade sarcoma</td>
<td>Rt temporal/posterior fossa</td>
<td>72 CGE/36</td>
<td>63.4/38</td>
<td>206</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Grade I meningioma</td>
<td>Lt cavernous sinus</td>
<td>50/25</td>
<td>50.4/28</td>
<td>37</td>
<td>10</td>
<td>None</td>
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<tr>
<td>7</td>
<td>Macroadenoma</td>
<td>Suprasellar</td>
<td>54/30</td>
<td>50.4/28</td>
<td>121</td>
<td>24</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

CGE = cobalt gray equivalents; RT = radiotherapy.
* This patient died of disease progression.
† This patient received proton therapy.

**TABLE 2. Radiotherapeutic and dosimetric characteristics of all targets**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Re-Irradiation GKI Prescription Dose</th>
<th>Isodose Line (%)</th>
<th>Dmax GKI</th>
<th>Dmean GKI</th>
<th>Cumulative Prescription Target Dose in EQD210 (Gy)*</th>
<th>Cumulative Mean Target Dose in EQD210 (Gy)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (Gy)/Fractions (no.)</td>
<td>EQD210 (Gy)*</td>
<td>Emax (Gy)*</td>
<td>Emean (Gy)*</td>
<td>GKI Target Vol (cm³)</td>
<td>GKI PCI</td>
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<tr>
<td>1</td>
<td>30/10</td>
<td>32.5</td>
<td>54</td>
<td>55.5</td>
<td>71.9</td>
<td>3.90</td>
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<tr>
<td>2</td>
<td>50.4/28</td>
<td>49.6</td>
<td>50</td>
<td>76.1</td>
<td>80.6</td>
<td>55.5</td>
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<td>3</td>
<td>50.4/28</td>
<td>49.6</td>
<td>52</td>
<td>96.9</td>
<td>108.7</td>
<td>66.5</td>
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<tr>
<td>4</td>
<td>45/25</td>
<td>44.3</td>
<td>50</td>
<td>90.0</td>
<td>102.0</td>
<td>63.5</td>
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<td>5</td>
<td>63.4/38</td>
<td>61.7</td>
<td>57</td>
<td>132.9</td>
<td>149.4</td>
<td>102.6</td>
</tr>
<tr>
<td>6</td>
<td>50.4/28</td>
<td>49.6</td>
<td>57</td>
<td>88.3</td>
<td>96.9</td>
<td>68.8</td>
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<tr>
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<td>49.6</td>
<td>57</td>
<td>88.3</td>
<td>96.8</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Median (IQR) NA | 49.6 (2.7) | 54 (6) | 88.4 (11.3) | 96.9 (16.7) | 66.6 (8.2) | 68.8 (8.46) | 6.58 (0.79) | 0.79 (0.15) | 2.63 (0.57) | 102.7 (4.2) | 121.1 (9.5) |

Mean ± SD | 48.1 ± 8.7 | 53.9 ± 3.2 | 89.7 ± 23.4 | 100.9 ± 24.8 | 66.1 ± 9.1 | 69.3 ± 19.6 | 11.7 ± 15.9 | 0.80 ± 0.10 | 2.80 ± 0.50 | 104.9 ± 13.0 | 125.8 ± 25.1 |

GI = gradient index; NA = not applicable; PCI = Paddick conformity index.
* All EQD2 values were calculated with the assumption of an α/β ratio of 10 Gy, which refers to EQD210.
fractions (Dmean EQD2 46 Gy) (Fig. 1A). The cumulative maximum EQD2 to his brainstem, right optic nerve, left optic nerve, and optic chiasm were 97 Gy, 65 Gy, 58 Gy, and 60 Gy, respectively. The patient also received 4 cycles of bevacizumab after GKI re-irradiation as an adjuvant treatment to mitigate the risk of radiation necrosis.

The patient did well after treatment without any significant toxicities. MRI surveillance showed initial disease response after re-irradiation through 11 months after treatment, at which time MR surveillance showed marginal recurrence. The patient did not receive salvage therapy and died 13 months after re-irradiation secondary to tumor progression.

Case 2
A young adult patient presented with a 1-year history of progressive blurry vision and dizziness. The patient had a complex solid and cystic mass, which was 2.8 cm, located within the pineal region, and causing obstructing hydrocephalus. Biopsy showed a papillary tumor that was graded intermediate between WHO grade II to III. The patient received fractionated radiotherapy with 54 Gy/30 fractions administered with a LINAC-based IMRT technique to the tumor with a margin.

The patient was clinically and radiologically stable for nearly 3 years until surveillance MRI revealed a locally recurrent lesion measuring 1.5 cm. Given the previous brainstem maximum dose of 54 Gy, the decision was made to administer fractionated re-irradiation to the gross disease with GKI in 50.4 Gy/28 fractions (Dmean EQD2 56 Gy) (Fig. 1B). The cumulative maximum EQD2 to the brainstem was 74 Gy. The patient tolerated treatment well, with fatigue and tiredness as acute side effects. At 22 months after re-irradiation, the patient had no signs of disease progression or late treatment toxicity.

Case 3
A young adult patient with a 4.6-cm, WHO grade II, midline frontal meningioma underwent subtotal resection and adjuvant radiotherapy with LINAC-based IMRT in 54 Gy/30 fractions administered to the residual tumor and surgical bed.

After 6 years of serial slow growth, the tumor began to compress the optic chiasm and visual field deficits manifested. After re-resection, 4.4 cm of residual disease extended from the olfactory groove to the tuberculum sellae. Given a previous maximum dose of approximately 53 Gy administered to the optic chiasm and nerves, re-irradiation with GKI was performed. The patient was treated with 50.4 Gy/28 fractions (Dmean EQD2 56 Gy) (Fig. 1C). The cumulative maximum EQD2 to the brainstem was 74 Gy. The patient tolerated treatment well, with fatigue and tiredness as acute side effects. At 15 months after re-irradiation, the patient was clinically well with no visual deficits and stable disease.

Case 4
An adult patient presented with sudden-onset headache and vomiting and had a 2.7-cm mass arising from the fourth ventricle. Craniotomy and gross-total resection revealed WHO grade II ependymoma. After 18 months of...
MRI surveillance, the patient was treated for local recurrence with LINAC-based IMRT administered in 54 Gy/30 fractions.

Approximately 7 years after radiation, surveillance MRI showed a 4-mm enhancing nodule consistent with recurrent disease at the obex of the fourth ventricle. The previous maximal brainstem dose was 45 Gy, and the patient was re-irradiated with 45 Gy in 25 fractions with GKI (Dmean EQD2 66 Gy) (Fig. 1D). The cumulative maximum EQD2 to the brainstem was 93 Gy. Acute toxicities were observed during GKI, with headache, ataxia, and syncopal episodes requiring hospital admission and

FIG. 1. GKI plans. The contours and isodose lines for re-irradiation with GKI administered to patients 1–7 (A–G, respectively), as shown in the axial, coronal, and sagittal planes of T1-weighted post–gadolinium enhanced MR images. Gross tumor volume is indicated in magenta. The yellow lines and green lines represent the prescription and 50% isodose lines, respectively.
dexamethasone. However, these acute effects were self-limited and resolved after GKI. Forty months after GKI reirradiation, local progression was observed and subsequently palliative management was pursued.

Case 5
A young adult developed progressive headaches and had a low-grade spindle cell neoplasm in the right skull base. The patient subsequently received proton therapy with 72 cobalt gray equivalents in 36 fractions to the residual tumor.

After 7 years, the patient progressed locally and underwent debulking subtotal resection. Pathology revealed a high-grade spindle cell neoplasm. Given the previous brainstem maximum point dose of 71 cobalt gray equivalents, the decision was made to offer re-irradiation using GKI. She was treated with 50.4 Gy/28 fractions, followed by a 2-phase cone-down approach that delivered an additional 9 Gy in 6 fractions twice a day followed by 4 Gy in 4 fractions twice a day. Therefore, the total tumor dose delivered was 63.4 Gy (Dmean EQD2 109 Gy). The cumulative maximum EQD2 from all radiotherapy courses administered to her brainstem was 111 Gy.

Seven months after reirradiation, the patient’s tumor was stable with resolving edema. Subsequently, progressive nodular enhancement at the area of residual disease raised concern for local recurrence or pseudoprogression. The patient was not symptomatic, and the decision was made to treat with systemic chemotherapy and assume tumor recurrence. The patient’s status remains under control. The presumed inflammatory effects resolved on subsequent imaging, and no adverse effects were observed through 12 months after GKI on temozolomide.

Case 6
An adult patient presented with left-sided facial paresis, left-sided ear fullness, tinnitus, and ataxia. She had a 3.7-cm extra-axial lesion in the left petroclival angle with mass effect on the brainstem and underwent subtotal resection. Pathology was consistent with a WHO grade I meningioma.

One year later, the patient was treated with LINAC-based IMRT with 50 Gy/25 fractions for disease progression. Slow progression was observed over the subsequent 8 years, with increasing mass effect on the brainstem. Given the previous maximum doses of 49 Gy administered to the brainstem, optic chiasm, and left optic nerve, the patient was re-irradiated with GKI in 50.4 Gy/28 fractions (Dmean EQD2 71 Gy) (Fig. 1F). The cumulative maximum EQD2 to the brainstem, right optic nerve, left optic nerve, and optic chiasm were 92 Gy, 47 Gy, 60 Gy, and 52 Gy, respectively. The patient tolerated treatment well without any significant acute or subacute adverse effects and was doing well 10 months after treatment without any significant toxicity.

Case 7
An adult patient was diagnosed with a pituitary macroadenoma and treated with surgery and adjuvant radiotherapy with LINAC-based IMRT in 54 Gy/30 fractions. After 11 years of clinical stability, the patient was diagnosed with progressive disease with a 3.2-cm recurrent tumor encroaching on the right optic nerve and chiasm. The previous maximum dose to the brainstem, optic chiasm, and right optic nerve was 54 Gy. The decision was made to proceed with re-irradiation to the enhancing tumor using GKI with 50.4 Gy/28 fractions (Dmean EQD2 69 Gy) (Fig. 1G). The cumulative maximum doses in EQD2 to her brainstem, right optic nerve, left optic nerve, and optic chiasm were 76 Gy, 103 Gy, 39 Gy, and 77 Gy, respectively.

The mean re-irradiation EQD2 to the residual pituitary gland was 17 Gy. The patient experienced extreme fatigue throughout treatment that resolved 6 months after GKI. After 2 years of follow-up, the disease had continued to decrease in size on serial MRI. The patient remains clinically stable and retains normal pituitary endocrine function.

Discussion
Re-irradiation of intracranial primary tumors presents a significant clinical challenge and is often the only means of effective salvage therapy. One of the barriers to re-irradiation is the lack of guidance with respect to the prescribed dose, fractionation scheme, and most importantly what dose limits to the OAR should be imposed. Re-treatment has been generally discouraged due to the fear of complications, including brainstem necrosis and optic neuropathy. However, with image guidance and novel frameless technologies allowing for maximal sparing of critical adjacent OARs, the ability to offer fractionated re-irradiation with radiosurgical dose distributions now exists.

We have presented 7 cases of high-risk, high-reward conventionally fractionated re-irradiation GKI treatments that administered high cumulative tumoral doses to primary brain tumors. We specifically developed this protocol to take advantage of the minimal PTV margin, which serves to reduce overall treatment volume, as compared with our LINAC-based PTV margins. The sharp dose gradients associated with GKI also allow for rapid dose falloff to limit exposure within adjacent OARs, with a high degree of conformity (Table 2). Fully fractionated (1.8–3.0 Gy/day) treatment serves to maximize safety with respect to late adverse effects given the relationship between increasing fraction size and risk of late toxicity, which is a fundamental principle of radiation oncology. The dose rate associated with cobalt-60 is also far less than that delivered with LINAC technology, which may have some effect on sparing neural tissue independent of tumor control. With respect to the dose delivered, GKI treatment represents inherent dose escalation because of the heterogeneous dose distribution and associated practice of prescribing to lower isodose lines (typically ranging from 50% to 60%) than otherwise would be prescribed with standard LINAC technology (typically ranging from 70% to 95%). These dosimetric properties are evident in our patient treatment characteristics, as summarized in Table 2. The local control observed in this small patient case series was encouraging, and we have yet to see any significant serious adverse effects despite the high cumu-
lative EQD2 (range 74–127 Gy) administered to at least 1 critical OAR per patient (Table 2).

Emerging experimental and clinical data suggest that normal central nervous system tissues can recover from previous radiation exposure to allow for re-irradiation. Early work on re-irradiation by Ang et al. suggested significant long-term recovery of occult radiation damage in rhesus monkey spinal cord. In these experiments, the initial radiation dose consisted of 44 Gy in daily 2.2-Gy fractions, and the animals were re-irradiated within 1 to 3 years to receive cumulative doses ranging from 83.6 to 110 Gy in 2.2-Gy/day fractions. The authors concluded that approximately 75% of the initial radiation damage had recovered at 2 years.10,11

Wong et al. summarized patients with re-irradiation myelopathy who received < 5 Gy per fraction for either treatment course. It was suggested that a cumulative biologically effective dose (BED) of 120 Gy was safe.12 Nieder et al. re-analyzed the literature and concluded, based on conventionally fractionated re-irradiation of the human spinal cord, that a cumulative BED of 135.5 Gy was safe if neither course exceeded 98 Gy and the time interval was not shorter than 6 months.13,14 Mayer and Sminia conducted a systematic review of 21 studies of brain re-irradiation and determined that radionecrosis risk increased at a cumulative EQD2 of 100 Gy.15 Recently, a large re-irradiation series of metastatic and primary intracranial tumors treated with LINAC technology was reported by Stiefel et al. A modest 4% rate of high-grade (3+) toxicities was observed, including 2 patients with grade 3–4 seizures and a third patient who died. The authors concluded that a cumulative EQD2 of 120 Gy was safe for normal brain tissue, and that 100 Gy and 75 Gy were safe for the brainstem and optic structures, respectively.16

In the current study, despite a median cumulative target mean EQD2 of 121 Gy, limited acute and subacute toxicities and no serious late adverse events were observed. For the OARs, the cumulative median (range) maximum point EQD2 to the brainstem, optic nerves, and optic chiasm were 91.56 (74.0–111.5) Gy, 58.94 (6.3–102.9) Gy, and 59.9 (36.7–127.3) Gy, respectively. In only 1 patient did cumulative exposure to a critical OAR exceed 120 Gy (patient 3 received EQD2 of 127.3 Gy to the optic chiasm). The median (range) time interval between irradiation courses was 88 (16–206) months. Therefore, our experience is consistent with the data from both the limited animal and clinical re-irradiation studies. The brainstem and optic structure limits proposed by Stiefel et al. are also consistent with our experience, but there may be room to be more aggressive when clinically needed, with the caveat that our patients were treated with GKI.19 Interestingly, the 1 patient with a re-irradiated pituitary macroadenoma (patient 7) retained normal pituitary function through 24 months after re-irradiation GKI, which suggests potential for recovery within glandular tissue.

With respect to dosimetric comparisons of GK technology, the benefits in terms of conformity and dose exposure have been reported by several groups. Han et al. reviewed 10 patients with 2 or more large brain metastases treated with LINAC-based HRSRS and retrospectively generated GK and CyberKnife (Accuray) plans for each patient. They found that, in comparison to LINAC-based HRSRS, GK-generated plans had much lower gradient indices and an approximately 20% lower volume of brain tissue receiving 20 Gy (V20).17 Similarly, Schelin et al. found that patients who received re-irradiation with GK for recurrent glioblastoma had V12 and V20 values that were 32.4% and 25.9% lower than those of the patients treated with LINAC plans.18 Cao et al. compared patients with large brain tumors who underwent HRSRS with different modalities, including GK, CyberKnife, volumetric modulated arc therapy, and proton therapy. GK plans had smaller gradient indices for treatment of brain metastases. However, this difference diminished with increasing target volume.19

Institutional experiences specific to re-irradiation using frameless GK technology have been reported but are limited to single-fraction SRS or HRSRS. McTyre et al. re-irradiated 5 tumors in 3 patients with HRSRS by using Perfexion GK equipped with the Extend frameless immobilization system (no cone-beam CT or infrared motion-gating system was used). They observed radiographic responses in all treated tumors and no radionecrosis events.20 Vulpe et al. treated 100 patients using GKI, and 14 lesions were re-irradiated with single-fraction SRS or HRSRS. This included 7 metastases, 3 meningiomas, and 1 case each of ependymoma, hemangiopericytoma, arteriovenous malformation, and glioblastoma. Most tumors had complete overlap with the previous 50% isodose line. In total, only 4 cases of grade 3+ toxicity were observed among the entire patient cohort, including muscle weakness, cerebral edema, intracranial hemorrhage, and encephalitis.21 One cannot associate the cumulative dose limits of the current series with these outcomes, as our results are specific to conventionally fractionated GKI re-irradiation.

To our knowledge, our series is the first to report detailed outcomes of patients who were re-irradiated with protracted and conventionally fractionated radiotherapy using GKI. We observed encouraging outcomes with respect to tumor control, with the caveat that prolonged follow-up will determine the ultimate efficacy and safety of this strategy. We acknowledge that late toxicities, including radionecrosis, may take years to develop. Nevertheless, no patient thus far has experienced any late serious adverse events, and all patients are receiving meticulous follow-up with serial imaging and clinical assessments. Our experience suggests that GKI-based fully fractionated re-irradiation is a feasible modality in this patient population.

We recognize the limitations of our study, which include the small sample size, mixed primary tumoral histologies, limited duration of median follow-up, and the usual caveats associated with retrospective studies. In particular, we caution that our estimates of cumulative maximum EQD2 administered to both the tumor and OARs are represented as the sums of the Dmax values and, therefore, these do not account for geographical variations in point dose between the original and re-irradiation plans. Furthermore, we acknowledge that although the de novo α/β ratio of nonmalignant intracranial tumors is thought to be lower than that of invasive cancers,22–24 this value is not well defined in the recurrent setting to account for a more
aggressive tumor biology and lack of radiosensitivity. Nevertheless, the results of our case series are encouraging for GKI as a treatment option for patients with progressive intracranial tumors in the setting of prior high-dose irradiation and proximity to dose-limiting critical OARs.

Conclusions

The current study provides a detailed overview of the treatment and outcomes specific to a cohort of patients with primary brain tumors, previously irradiated with LINAC technology, who underwent GKI re-irradiation with conventional fractionation. Further investigation on a larger scale with a defined clinical trial is needed to confirm efficacy and safety, but this modality may be a feasible option in the setting of limited available treatment options given the encouraging outcomes and overall favorable safety profile.

References


Disclosures

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Author Contributions
Conception and design: Sahgal, Yan. Acquisition of data: Yan, Holden. Analysis and interpretation of data: Yan, Detsky, Tseng, Ruschin. Drafting the article: Sahgal, Yan, Holden, Detsky, Tseng, Ruschin. Critically revising the article: all authors. Reviewed submitted version of manuscript: Sahgal, Yan, Detsky, Tseng, Soliman, Myrehaug, Husain, Das, Yeboah, Lipsman, Ruschin. Approved the final version of the manuscript on behalf of all authors: Sahgal. Statistical analysis: Yan, Myrehaug, Husain, Das, Yeboah, Ruschin. Administrative/technical/material support: Sahgal, Soliman, Myrehaug, Husain, Das, Yeboah. Study supervision: Sahgal, Soliman, Ruschin. Figure generation: Holden.

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