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Hypofractionated Gamma Knife Radiosurgery: Institutional Experience on Benign and Malignant Intracranial Tumors

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Abstract. *Background/Aim: We investigated the treatment outcomes and complications associated with hypofractionated GKRS for the treatment of benign and malignant intracranial tumors. Patients and Methods: Patients with intracranial tumors not candidate or refusing surgery were evaluated to assess eligibility to undergo hypofractionated Gamma Knife radiosurgery (GKRS). Targeted volumes were calculated using the GammaPlan® workstation, and GKRS protocols were delivered with 3 or 5 daily fractions and a maximal total dose of 25 Gy. The thermoplastic mask was used to immobilize the patient's head without pin-based fixation frames. Results: A total of 41 patients, affected with 6 different histologies, were treated and followed-up for a median of 12 months (range=4-24 months). Meningiomas were the most common tumors (33, 80.5%), followed by brain metastases (4, 9.7%). At last follow-up, 33 patients (80.5%) had stable disease, 8 tumor regression (19.5%), and 0 tumor progression. No acute radiation toxicity was observed. Death was reported in 3 patients (7.3%) due to malignant tumor progression. Conclusion: Our hypofractionated GKRS protocol proved to be effective and safe in the treatment of patients with benign and malignant intracranial tumors. Local tumor control was achieved in all patients, with 8 patients showing tumor regression and no cases of acute radiation toxicity.*

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Since its conception in 1951, Gamma Knife radiosurgery (GKRS) raised the interest of the international neuro-oncology community (1, 2). GKRS may treat a variety of intracranial tumors, vascular malformations, and functional

disorders by delivering high radiation beams to specific targets, while minimizing doses to neighboring structures. Advances in stereotactic imaging and computer software further enhanced treatment planning and responsiveness (3, 4). In the current neuro-oncology era, GKRS is frequently considered as upfront and adjuvant treatment in combination with surgical resection, or as a minimally invasive alternative in patients not eligible to surgery (5-10).

Early GKRS units delivered single-fraction treatments using burdensome rigid-based frames, which immobilized the patient's head and defined the stereotactic coordinates (11). These systems prevented the split of irradiation in multiple fractions, delivering high radiation doses to selected targets with greater risks of adverse radiation events (12, 13). The recently introduced Leksell Gamma Knife® Icon™ overcame these hurdles (14). The system, mounted with a cone beam CT and an infrared-based high-definition motion management camera, tracks patient's movements in real-time and facilitates frameless fractionated GKRS (15). While single-fraction GKRS is mostly limited to small lesions manageable in single sessions, hypofractionated GKRS allows the treatment of multiple and/or larger lesions, especially brain metastases, which have proven to be biologically more responsive to fractional radiation therapies (6). In addition, by distributing irradiation into multiple beams with lower doses, hypofractionated GKRS protocols may be favored for treating deep-seated lesions localized within or around critical structures, such as the brainstem (5).

In the current study, we present our single-institution experience with the use of hypofractionated GKRS in the treatment of patients with benign and malignant intracranial tumors, including meningiomas, brain metastases, glioblastoma, schwannoma, ependymoma, and hemangioma.

Patients and Methods

A retrospective review of an institutional review board-approved prospective GKRS database was conducted at our institution in accordance with the Declaration of Helsinki. Patients included in this observational study were treated with hypofractionated GKRS for benign and malignant intracranial tumors not eligible to surgical resection. Data reported in this observational study were extracted from patients' clinical files, including patients' demographics, tumors' locations, pre- and post-GKRS tumor volumes, GKRS protocols, follow-ups, and complications. Written consent for this study was not sought due to the retrospective study design. The following study was devised in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File 1).

Clinical and neuroimaging assessments. Patients were referred to our Gamma Knife center from different national hospitals as our institution is one of the few in Italy equipped with a Leksell Gamma Knife® Icon™ . Upfront GKRS was offered to patients who satisfied ≥1 of the following criteria: 1) refused surgery; 2) had severe cardiorespiratory comorbidities; 3) presented with large, multiple, recurrent or deep-seated lesions not amenable to surgical resection. In some cases, adjuvant GKRS protocols were also offered to patients with post-surgical residual tumors bordering with critical neuro-vascular structures (*e.g.*, cavernous sinus or brainstem). A multidisciplinary board of neurosurgeons, radiotherapists, and physicists assessed patients' eligibility and obtained informed consent. All patients underwent preoperative neuroimaging assessment consisting of gadolinium-enhanced head magnetic resonance imaging (MRI) scans, and additional head ^{68}Ga-DOTATOC (DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide) positron emission tomography/computed tomography (PET/CT) studies were obtained only in patients presenting with meningiomas. Tumors were manually contoured on MRI scans obtained with a 1.5T scanner (Philips Achieva, Amsterdam, Netherlands) upon the following settings: T1W 3D-TFE (turbo field echo) TR/TE 7.5/3.4; slice thickness=1 mm, FA (flip angle)=8°; TFE factor=240; and FOV=240×240. Pre- (baseline) and post-GKRS tumor volumes were automatically calculated after the manual contouring. The quantitative volumetric method described by Harrison *et al*. (16) was applied to measure tumor responses after GKRS treatments. Post-GKRS tumor responses were classified as following: progression if the tumor volume increased ≥15% from baseline; regression if the tumor volume decreased ≥15% from baseline; stable if tumor volume changed (increased or decreased) <15% from baseline.

Gamma Knife protocol. The Leksell GammaPlan® (Elekta AB, Stockholm, Sweden) was employed on preoperative T1-contrast MRI scans to highlight critical structures, select target volumes, and set the radiation doses to be administered. The hypofractionated protocol adopted at our institution consists of 5 fractions, with approximate doses of 4 Gy for the first fraction and 5 Gy for the others, both at 50% isodose, and maximal doses of 20-25 Gy. The Leksell Gamma Knife® Icon™ (Elekta AB, Stockholm, Sweden) was operated in all procedures. Treatments are frameless and performed by placing a thermoplastic mask on the patients' heads. During the treatment, the patient's position is constantly monitored by an infrared-based high-definition motion management camera with a movement sensibility of 0.15 mm, which controls and shuts off the beam administration when detected movements become insufferable. The image guidance system is composed of a stereotactic MRI scan and an integrated stereotactic cone beam CT scan and sets coordinates in 3D after co-registrations with preoperative MRI images. The device analyzes data on image guidance and generates up to 192 low-intensity radiation beams from Cobalt-60 sources converging with high accuracy on preselected targets. The 192 cobalt-60 beams are not coplanar, thus adjustable to compensate for minimal patient movements and achieve a perfect 6D positioning.

Statistical analysis. The software SPSS V.25 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. Continuous variables are presented as means or medians and ranges, and categorical variables as frequencies and percentages. The time intervals between GKRS treatments and patient's death [overall survival (OS) curve] were estimated with the Kaplan–Meier method. Two-sample weighted *t*-test was performed to assess differences between pre- and post-GKRS tumor volumes. The Pearson correlation test was run to assess whether post-GKRS changes in tumor volumes correlated with per-patient clinical and treatment characteristics. All analyses were bilateral and *p*-values <0.05 were considered statistically significant.

Results

Patient population. We identified 41 consecutive patients referred at our Gamma Knife Center between May 2018 and April 2021 (Table I). Median age was 68 years (range=33-85 years), and most patients were males (22, 53.7%). Tumor diagnoses were histologically confirmed in patients with prior surgical resection and/or with recurrent lesions. In patients with a history of primary cancers, secondary brain metastases were suspected on the basis of clinical and neuroimaging findings. A heterogeneous group of lesions were treated: 33 meningiomas (80.5%), 4 brain metastases (9.7%), 1 temporal ependymoma (2.4%), 1 frontal glioblastoma (2.4%), 1 sellar/parasellar hemangioma (2.4%), and 1 trigeminal schwannoma (2.4%). As regards the meningiomas, the most frequent locations were the clinoid (5, 15.1%), parasagittal angles (4, 12.1%), olfactory groove (3, 9.1%), and sphenoidal wing (3, 9.1%). Of 33 patients with meningioma, nine were operated on. Five of them were histologically grade I WHO (Ki-67 <3%), three were atypical grade II WHO, and only one was anaplastic tumor and was treated for progression after conventional radiotherapy. The patient with hemangioma was also histologically confirmed. The ependymoma's patient had already been operated three years earlier and histology showed ependymoma (grade II WHO). He was then radiosurgically treated for local progression after conventional treatment. Among patients with meningiomas, all non-operated patients were apparently symptom-free except two patients with cavernous sinus meningioma complaining of diplopia and one patient with petrous bone meningioma complaining of hypoacusis. Four of the nine operated patients with meningioma had hemiparesis and balance disorders, progressively improving in three of them. The patient with the hemangioma was symptom-free and the one with ependymoma had seizures. As we reported, all the treated patients showed short-lasting brain swelling without any clinical change and resolving with steroids. One non-operated patient with parasagittal meningioma developed brain swelling with slight transient hemiparesis, which regressed after one month of steroids.

Gamma knife settings and target volumes. In total, 161 daily fractions were delivered among all included patients, with a median of 3 fractions per-patient. Twenty-two patients received hypofractionated GKRS in 3 daily fractions (median volume=10.9 cm^3), while 19 patients in 5 daily fractions (median volume=11.9 cm^3). The median per-fraction dose was 6.0 Gy (range=4.7-6.7 Gy). All hypofractionated GKRS were delivered at a 50% isodose line, with a median total maximal dose of 23.5 Gy (range=18.0-26.1 Gy). The median targeted volume for the whole cohort was 11.4 cm^3 (range=0.6-35.1 cm^3), higher in patients with meningiomas (11.6 cm3, range=0.6-35.1 cm^3) compared to patients with brain metastases (10.3 cm^3, range=1.0-14.2 cm^3), which represented the two most common treated lesions.

Table I. *Summary of clinical characteristics and outcomes of all 41 patients treated with hypofractionated Gamma Knife radiosurgery.*

Characteristics	Value
Cohort size	41
Demographics	
Median age (range) (years)	68 (33-85)
Male (no., %)	22 (53.7%)
Female (no., %)	19 (46.3%)
Tumor diagnosis	(No., %)
Meningiomas	33 (80.5%)
Brain metastases	4 (9.7%)
Ependymoma (Temporal)	1 (2.4%)
Glioblastoma (Frontal)	1 (2.4%)
Hemangioma Sellar/Parasellar)	1 (2.4%)
Schwannoma (Trigeminal)	1 (2.4%)
Location of meningiomas (n=33)	(No., %)
Clinoid	5 (15.1%)
Parasagittal	4 (12.1%)
Olfactory groove	3 (9.1%)
Sphenoid wing	3 (9.1%)
Cavernous sinus	2 (6.1%)
Parasellar	2 (6.1%)
Petrous bone	2 (6.1%)
Spheno-petrosal	2 (6.1%)
Tentorium	2 (6.1%)
Frontopolar	1 (3%)
Planum sphenoidale	1 (3%)
Pterional	1 (3%)
Sellar	1 (3%)
Spheno-cavernous	1 (3%)
Spheno-orbital	1 (3%)
Superior sagittal sinus	1 (3%)
Temporal	1 (3%)
Gamma Knife radiosurgery protocol	
Fractions	
Total	161
Per-patient, median (range)	3 (3-5)
Dose (Gy)	
Maximal, median (range)	23.5 (18.0-26.1)
Per-fraction, median (range)	6.0 (4.7-8.7)
Tumor volumes (cm^3)	Median (range)
Baseline (pre-Gamma Knife radiosurgery)	11.4 (0.6-35.1)
At final follow-up (post-Gamma Knife radiosurgery)	10.5 (0.6-35.1)
Volumetric response to Gamma Knife radiosurgery	
Overall volume reduction in cm^3, median (range)	0.2 (0-6.9)
Overall volume reduction in %, median (range)	1.5 (0-60.5)
Stable	
No., %	33 (80.5%)
Volume change, median (range) (cm^3)	0.1 (0-6.0)
Volume change, median (range) (%)	1.3 (0-10.3)
Regression	
No., %	8 (19.5%)
Volume change, median (range) (cm^3)	2.1 (0.3-6.9)
Volume change, median (range) (%)	31.1 (15.4-60.5)
Progression	
No., %	0 (0%)
Follow-up, median (range) (months)	8.0 (4.0-24.0)
Transient complications (<1 month)	No., %
Brain swelling	41 (100%)
Hemiparesis	1 (2.4%)
Status	No., %
Alive	38 (92.7%)
Dead	3 (7.3%)

Table II. *Correlations between tumor volume changes post-Gamma Knife radiosurgery and per-patient clinical and treatment characteristics.*

Variables*	Pearson's R correlation	R^2 linear	*p*-Value
Number of fractions	–0.058	0.003	0.718
Dose per-fraction (Gy)	0.184	0.034	0.249
Maximal total dose (Gy)	0.108	0.012	0.503
Baseline tumor volume (cm^3)	0.073	0.005	0.651
Time of post-treatment follow-up (months)	0.170	0.029	0.289

*Pearson's tests correlated volume changes (cm^3) post-Gamma Knife radiosurgery with each variable. *p*-Value <0.05 was considered statistically significant for all tests.

Treatment outcomes. Patients were followed-up for a median of 12 months (range=4-24 months) after receiving the last GKRS fraction. Lesions were monitored at each follow-up visit, and the volumes calculated at the last available follow-up were reported in this study (Supplementary File 2). The median post-GKRS tumor volume for the whole cohort was 10.5 cm^3 (range=0.6-35.1 cm^3), higher in patients with meningiomas (10.8 cm^3, range=0.6-35.1 cm^3) compared to patients with brain metastases (4.3 cm^3, range=0.7-11.3 cm^3). Overall, post-GKRS median tumor volume reduction was 0.2 cm^3 (range=0-6.9 cm^3) or 1.5% (range=0-60.5%). We found no significant difference between pre-GKRS and post-GKRS tumor volumes for the whole cohort (p=0.332), and separately for patients with meningiomas (p=0.771) or brain metastases (p=0.133).

Tumors were stable in 33 patients (80.5%), with a median tumor volume change of 0.1 cm^3 (range=0-6 cm^3) or 1.3% (range=0-10.3%). Tumor regression was described in 8 patients (19.5%), with a median tumor volume reduction of 2.1 cm^3 (range=0.3-6.9 cm^3) or 31.1% (range=15.4-60.5%). Of note, no patient showed tumor progression at last follow-up. Correlations between post-GKRS tumor volume changes and per-patient characteristics were calculated and presented as scattered plots (Supplementary File 3). Volumetric changes were not statistically correlated with per-patient number of fractions (r:–0.058; p=0.718), per-fraction dose (Gy) (r:0.184; p=0.249), total maximal dose (Gy) (r:0.108; p=0.503), baseline tumor volume (cm^3) (r:0.073; p=0.651), and time of post-treatment follow-up (months) (r:0.170; p=0.289) (Table II).

Supplementary File 4 shows the survival curve for the whole cohort. The vast majority of patients were alive at the end of this study (38, 92.7%). Death was reported in 3 patients (7.3%): the first patient was treated for glioblastoma recurrence and died at 6-months post-GKRS due to tumor progression; the second patient was treated for multiple brain metastases and died at 9-months post-GKRS due to systemic metastatic spread; the third patient was treated for anaplastic meningioma and died at 14-months post-GKRS due to the deteriorating clinical conditions related to old age.

In our cohort, some GKRS-related complications were also described. All 41 patients presented with various degrees of post-treatment transient brain swelling, promptly resolved with steroids. In 1 patient (2.4%) treated for parasagittal meningioma, the brain edema led to transient contralateral hemiparesis after the last GKRS procedure, which regressed in <1 month with steroids. Of note, no permanent GKRS-related complications were found.

Discussion

In this retrospective observational study, we report our single-institution experience with the use of hypofractionated GKRS for the treatment of 41 patients affected by various benign and malignant intracranial tumors. We found that hypofractionated GKRS is a safe and effective therapeutic option both upfront, in patients not eligible to undergo surgery, and adjuvant, in patients with residual tumors not amenable to complete surgical resection. All patients treated with hypofractionated GKRS showed long-term local tumor control and low rates of transient GKRS-related complications, easily and promptly manageable with steroids.

Despite the well-established benefits of radiotherapy in neuro-oncology, radiation-related complications pose significant risks, and tolerable radiation doses to normal brain tissue highly depend on the adopted radio-surgical protocols (17). The radiation doses delivered to the periphery of the targeted lesions also affect the surrounding brain tissue, and steeply increase in a nonlinear function with the target size, escalating the risks of radiation injury in the treatment of larger lesions (18). On these terms, the sharp dose fall-off of GKRS represents one of the main advantages over traditional radiotherapy techniques, such as CyberKnife and intensity-modulated radiotherapy, delivering high central target doses, while safely sparing the bordering healthy brain tissue (19). The latest introduction of non-coplanar arcs beam techniques further improved GKRS planning in treating larger lesions, rotating about the target isocenter and delivering focused sector beam-based intensity modulated GKRS irradiations with limited doses on the periphery (20). Although the

maximal brain-tolerable radiation dose has yet to be defined, hypofractionated GKRS treatments represent the currently safest alternatives by providing lower irradiation to the healthy brain tissue surrounding the targeted lesion (21). This is of special interest for targeting lesions close to critical neuro-vascular structures, such as the optic pathways and the cavernous internal carotid artery, or larger in size (22, 23). In addition, while previous GKRS systems used burdensome pin-based head frames to fix the patient's head, which needed to be repositioned at every procedure, the newer Leksell Gamma Knife® Icon™ employs a non-invasive and relocatable thermoplastic head mask (24). Also, the integrated GammaPlan® workstation minimizes the risk of reduction of radiation beams accuracy by merging the pre-operative volumetric MRI studies with the cone beam CT scans obtained during the GKRS sessions (14, 15).

In this study, we present the largest series of patients with both benign and malignant intracranial tumors – for a total of 6 different histologies – treated with hypofractionated GKRS using the latest Leksell Gamma Knife® Icon™ . A total of 41 patients were treated for various neoplasms, the most frequent being meningiomas (33, 80.5%) and brain metastases (4, 9.7%). The targeted tumors were mostly large, multiple, recurrent, or post-craniotomy residual surrounding critical neuro-vascular structures, and/or affecting patients not candidate or refusing surgery. All lesions were also not eligible to undergo single-fraction GKRS, suggesting the superior feasibility of hypofractionated GKRS and its valuable role in neuro-oncology. Indeed, the delivery of hypofractionated GKRS to recurrent or post-surgery residual tumors is of great importance, since it may provide a powerful adjunct to the standard therapeutic protocols, offering effective treatments with limited risks of radiation damage (15). Our findings support the safety and effectiveness of such protocols, as we achieved good long-term local tumor control in all treated patients (median follow-up time 12 months) with modest rates of transient complications, mainly caused by post-GKRS brain edema that completely regressed with corticosteroid treatment. Of interest, no acute radiation toxicity reactions were found. Our survival rates were also consistent with the current literature, with 3 patients dead at last follow-up due to malignant tumor progression or systemic spread, thus not related to radiation treatments (25).

Due to the lack of extensive experiences on hypofractionated GKRS for the treatment of intracranial tumors, unique guidelines have yet to be defined, and current data are still limited and heterogeneous. Hence, we devised our protocol on the basis of the few studies in the literature that reported favorable outcomes in treating intracranial tumors (26, 27). The reported number of fractions ranged from 3 to 5, and the between-fraction time interval from days to months, depending on the center experience and lesion characteristics (28). In our cohort, we delivered 3 or 5 GKRS fractions per-patient, with a median dose of 6 Gy (range=4.7-6.7 Gy), which has been correlated with good tumor control (27). In line with previous studies, we also set the isodose line at 50% for all procedures, achieving a median maximal total dose of 23.5 Gy (range=18.0-26.1 Gy) (19, 26). The targeted tumor volumes of our cohort were highly variable, ranging from 0.6 to 35.1 cm3. These findings are explained by the all-round eligibility criteria set for hypofractionated GKRS: lower targeted volumes were related with residual post-craniotomy tumors, bordering critical structures not amenable to surgical resection, whereas larger targeted volumes linked to lesions and/or patients not eligible to undergo surgery. Regardless of baseline targeted tumor volumes, post-GKRS neuroimaging at follow-up documented stable disease in most patients (33, 80.5%), and tumor regression in the remaining cases (8, 19.5%), not detecting any case of tumor progression. Considering the well-known indications for multisession GKRS for large tumors and near-OAR lesions, we selected a multisession procedure even for small tumors (<1 ml) if they were located close to critical structures or in case of small recurrent glioblastoma. In our set of four patients, two of them had small clinoid meningiomas, which were located very close to the optic canal entrance and the patients were symptoms-free; the third one had a small post-craniotomy remnant of a tentorial meningioma, and the last one had a very small recurrent glioblastoma (IDH-wild, MGMT-wild). In cases of meningiomas, we selected multisession GKRS and each patient received 3 daily fractions using a per-fraction dose of 6 Gy at 50% isodose line with a maximal dose of 18 Gy. The recurrent glioblastoma was treated instead with a 3 daily fractions session using a per-fraction dose of 7.5 Gy at 50% isodose line and maximal dose of 22.5 Gy. As local tumor control represents the primary treatment goal in patients undergoing GKRS, our findings suggest the high effectiveness of hypofractionated protocols (29, 30). Regarding BED, the marginal dose used per-fraction was calculated referring to the marginal dose usually used in the single fraction treatment. This allowed us to deliver a therapeutic dose from a radiobiological point of view. In addition, tumor regression was achieved in 3 patients with benign tumors and 5 with malignant lesions – all of 4 patients with brain metastases and 1 patient with anaplastic ependymoma – further highlighting the importance of such strategy. We note that post-GKRS tumor volume changes were not correlated with the number of fractions, per-fraction and maximal total doses, baseline tumor volume, and follow-up time, which may support the favorable replicability of our protocol; however, it still needs to be confirmed with larger and prospective studies. In our cohort of patients, 8 of them showed a change in tumor volume during the follow-up after treatment. These were the four patients affected by meningioma, three patients with brain metastasis, and the patient with parasellar hemangioma. Patients with metastases showed a partial response (<50% volume) after 4 months, persisting at last follow-up; the hemangioma patient showed a 50% volume

reduction at 18 months, as predictable. The patients with meningioma showed just slighter tumor volume reduction. They showed a 17% reduction at 24 months follow-up (from 14 cm^3 to 11.5 cm^3). Considering the few data still available regarding multisession GKRS for intracranial tumors, the present case series offers a follow-up of 1 year, which is sufficient to rate its safety and efficacy that could be considered as a helpful tool in the management of these neuro-oncological patients.

Based on our experience, we noted some small caveats with hypofractionated GKRS protocols and present here some insights. First, the lesions sited at the extremities of the radiation field – *i.e.*, too lateral or too cranial/caudal – may be difficult to be targeted, thus limiting GKRS's feasibility. This can be preoperatively simulated with the GammaPlan®, and, in some cases, may be overcome by merging pre-operative volumetric MRI studies with the cone beam CT scans. Second, extended hypofractionated GKRS techniques – *i.e.*, delivering peripheral radiation beams to facial structures – may lead to increased risks of teeth deformation and malocclusion (31). The correct positioning of the thermoplastic mask may reduce those risks, allowing to treat patients without intact upper palate and dentition, previously required with the use of older GKRS systems. Third, the patient-perceived claustrophobia may represent a small limitation in using the thermoplastic mask. Of interest, this reaction is not predictable, as some patients with trait anxiety may tolerate the treatment while some patients without trait anxiety may be in distress and prefer to abort the session. Hence, we suggest that each GKRS fraction should not exceed 20-25 minutes to minimize patient's discomfort.

Limitations. The main limitation of the present study is represented by its retrospective and single-institution design, which is known to be prone to patient selection bias. The relatively short follow-up is also noted, owed to the limited availability of the Leksell Gamma Knife® Icon™ system at our institution (approximately 3 years). The heterogeneity of treated tumors, with related differences in histology and radiosensitivity, may lead to some confounders in accurately evaluating the effect of hypofractionated GKRS. However, this study needs to be considered as a preliminary experience, providing new insights on the role of hypofractionated GKRS in neuro-oncology, which may guide and need to be confirmed by further prospective and multi-institutional investigations.

Conclusion

GKRS is a well-established tool that provide local tumor control as adjuvant treatment in post-surgical residual and recurrent lesions, or as upfront treatment in selected cases. Our study joins recent reports with the aim of validating hypofractionated GKRS protocols as valuable alternatives to surgery in neuro-oncology. All of 41 patients treated in our cohort for various intracranial tumors showed optimal local tumor control, coupled with 8 cases of tumor regression, few transient complications and no acute radiation toxicity. Hence, hypofractionated GKRS demonstrated great importance in the daily neuro-oncology practice, allowing neurosurgeons and radiotherapists to treat patients refusing surgery or too fragile to undergo it, patients with multiple tumors and/or located close to critical neuro-vascular structures, and also patients with a history of multiple craniotomies for tumor recurrence or metastatic tumor spread.

Supplementary Material

Available at: https://www.dropbox.com/sh/ihbyiq8w4wf9xm3/AAA4wG6klSNSWttsqdw_PJAUa?dl=0

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Francesco Inserra: Conceptualization, Methodology, Writing – Original draft preparation; Fabio Barone: Conceptualization, Methodology, Writing – Original draft preparation; Paolo Palmisciano: Methodology, Data analysis, Writing – Original draft preparation; Gianluca Scalia: Resources, Writing – Reviewing and Editing; Valerio Da Ros: Resources, Writing – Reviewing and Editing; Ahmed Abdelsalam: Resources, Writing – Reviewing and Editing; Antonio Crea: Resources, Writing – Reviewing and Editing; Maria G. Sabini: Resources, Writing – Reviewing and Editing; Santino O. Tomasi: Resources, Writing – Reviewing and Editing; Gianluca Ferini: Resources, Writing – Reviewing and Editing; Rosario Maugeri: Resources, Writing – Reviewing and Editing; Lidia Strigari: Resources, Writing – Reviewing and Editing; Giuseppe E. Umana: Methodology, Resources, Writing – Reviewing and Editing, Supervision.

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