Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study

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OBJECTIVE Hemangiopericytomas (HPCs) are rare tumors widely recognized for their aggressive clinical behavior, high recurrence rates, and distant and extracranial metastases even after a gross-total resection. The authors report a large multicenter study, through the International Gamma Knife Research Foundation (IGKRF), reviewing management and outcome following stereotactic radiosurgery (SRS) for recurrent or newly discovered HPCs.

METHODS Eight centers participating in the IGKRF participated in this study. A total of 90 patients harboring 133 tumors were identified. Patients were included if they had a histologically diagnosed HPC managed with SRS during the period 1988–2014 and had a minimum of 6 months’ clinical and radiological follow-up. A de-identified database was created. The patients’ median age was 48.5 years (range 13–80 years). Prior treatments included embolization (n = 8), chemotherapy (n = 2), and fractionated radiotherapy (n = 34). The median tumor volume at the time of SRS was 4.9 cm³ (range 0.2–42.4 cm³). WHO Grade II (typical) HPCs formed 78.9% of the cohort (n = 71). The median margin and maximum doses delivered were 15 Gy (range 2.8–24 Gy) and 32 Gy (range 8–51 Gy), respectively. The median clinical and radiographic follow-up periods were 59 months (range 6–190 months) and 59 months (range 6–183 months), respectively. Prognostic variables associated with local tumor control and post-SRS survival were evaluated using Cox univariate and multivariate analysis. Actuarial survival after SRS was analyzed using the Kaplan-Meier method.

RESULTS Imaging studies performed at last follow-up demonstrated local tumor control in 55% of tumors and 62.2% of patients. New remote intracranial tumors were found in 27.8% of patients, and 24.4% of patients developed extracranial metastases. Adverse radiation effects were noted in 6.7% of patients. During the study period, 32.2% of the patients (n = 29) died. The actuarial overall survival was 91.5%, 82.1%, 73.9%, 56.7%, and 53.7% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. Local progression–free survival (PFS) was 81.7%, 66.3%, 54.5%, 37.2%, and 25.5% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. In our cohort, 32 patients underwent 48 repeat SRS procedures for 76 lesions. Review of these 76 treated tumors showed that 17 presented as an in-field recurrence and 59 were defined as an out-of-field recurrence. Margin dose greater than 16 Gy (p = 0.037) and tumor grade (p = 0.006) were shown to influence PFS. The development of extracranial metastases was shown to influence overall survival (p = 0.029) in terms of PFS; repeat (multiple) SRS showed additional benefit.
EMANGIOPERICYTOMAS (HPCs) are uncommon, accounting for 0.4% of all primary intracranial tumors and 2.4% of meningeal tumors.17,23,41,48 HPCs resemble meningiomas in some aspects, yet substantially differ in others, being derived from fibrohistiocytic precursor cells and exhibiting molecular changes that are distinct from meningiomas. HPC is a meningeal tumor widely recognized for its aggressive clinical behavior, with high recurrence rates and distant extracranial metastases even after gross-total resection (GTR).6,35 The significant vascularity of HPCs and frequent involvement with adjacent dural sinuses and cranial osseous components can make surgical extirpation a challenging and at times unrealistic goal. Still, the initial treatment of larger intracranial HPCs is resection. Surgery offers immediate relief of related mass effect and provides tissue confirmation of diagnosis. Recent reports of surgical outcome offer a dismal 90% recurrence rate, with recurrence occurring as early as 7 months after the initial treatment.4,5,49 Combined treatment consisting of GTR and adjuvant external beam radiotherapy (EBRT) was reported to convey a mean survival of 84 months from time of diagnosis.24 Recurrence rates after such aggressive initial management combining GTR with EBRT have been as high as 30%.10 This high propensity for progression makes identifying the optimal management an open question.

Upon HPC recurrence or progression, adjuvant treatment is generally employed. Chemotherapeutic regimens have provided questionable benefit.3,13 Due to the potential for residual and recurrent tumor, stereotactic radiosurgery (SRS) is well suited for postoperative adjuvant therapy, particularly for inaccessible locations.45 The role of Gamma Knife (Elekta AB) and CyberKnife (Accuray) SRS in the treatment of HPCs has been previously described, with tumor control rates ranging from 46% to 100%.7,8,10,11,13,21,29,31,39,43,47 However, published reports have largely been small, single-center retrospective series, with only a few case series exceeding a cohort of 20 patients, limiting the statistical validity of any analysis (Table 1).32,39

We report on a large cohort, originating from a multicenter effort, through the International Gamma Knife Research Foundation (IGKRF), in an attempt to study outcomes of Gamma Knife radiosurgery (GKRS) for recurrent or newly discovered HPCs after resection.

Methods

Patient Population

Eight medical centers participating in the IGKRF obtained individual institutional review board approvals to participate in this study. A total of 90 patients with intracranial HPCs managed at least in part by GKRS were identified. At each center, retrospective clinical outcome analysis of Gamma Knife patients with HPCs was performed. The following centers contributed data for this study: University of Pittsburgh (30 patients), University of Virginia (22 patients), Barrow Neurological Institute (16 patients), National Yang-Ming University in Taipei, Taiwan (6 patients), Université de Sherbrooke (6 patients), Cleveland Clinic (5 patients), New York University (3 patients), and Beaumont Medical Center (2 patients). The clinical charts of patients harboring HPCs who underwent GKRS between 1988 and 2014 were evaluated by clinicians at each center for study inclusion. A database with selected variables was created and sent to the participating centers. Investigators at the participating centers reviewed the medical records of their patients, entered the data in the spreadsheet, and deleted all patient identifiers from the database. Pooled and de-identified data were screened by the IGKRF clinical trials coordinator for errors. Data were verified for compliance with protection of patient information. Any uncertainties or ambiguities in the data were addressed to investigators at the respective contributing center.

Patients were included in the study if they had a histologically diagnosed HPC. GKRS was not used as an upfront treatment for any patient in this cohort. A minimum of 6 months’ clinical and radiological follow-up was required for inclusion. Criteria included a medical history for HPC and an intracranial extraaxial tumor with MRI and/or CT imaging features most consistent with an HPC. The neuroimaging features included avid contrast enhancement, absence of calcification and hyperostosis, invasion of the skull, multiple flow voids seen on MRI, corkscrew arteries, and a narrow dural base of attachment. Demographic, medical, and clinical characteristics of the patients at different time points were logged. Detailed clinical and radiological presentations as well as outcome parameters were recorded. Neurological examination findings, complications, and deficits were recorded.

Cohort Overview

The specific patient and tumor attributes are detailed in Table 2. All patients in this series had histological evidence of HPC and had previously undergone at least 1 open surgical treatment for their intracranial disease prior to initial GKRS. Once diagnosis was made, GKRS was used for patients with residual or recurrent disease at the site of the original resection or for regional or distant intracranial disease recurrences of the HPC. HPCs have a predilection for such recurrences.

CONCLUSIONS SRS provides a reasonable rate of local tumor control and a low risk of adverse effects. It also leads to neurological stability or improvement in the majority of patients. Long-term close clinical and imaging follow-up is necessary due to the high probability of local recurrence and distant metastases. Repeat SRS is often effective for treating new or recurrent HPCs.

https://thejns.org/doi/abs/10.3171/2016.1.JNS152860

KEY WORDS hemangiopericytoma; stereotactic radiosurgery; Gamma Knife; multicenter study
Ninety patients harboring 133 intracranial HPCs were included in the cohort; the patients' median age was 48.5 years (range 13–80 years) and 55.6% were male (n = 50). Most of the patients in the cohort had a single HPC lesion (78.9%, n = 71). Two tumors were noted in 11.1% of patients (n = 10), 3 tumors in 2.2% (n = 2), and more than 3 tumors were noted in 7.8% (n = 7). All patients underwent at least 1 open cranial surgery for treatment of the HPC prior to GKRS (median number of operations 1, range 1–6). Thirty-four patients (37.8%) received pre-GKRS radiotherapy, with a median total prescribed dose of 54 Gy (range 15–64 Gy). Eight patients (8.9%) underwent prior embolization. Pre-GKRS chemotherapy was prescribed for 2 patients (2.2%).

Neurological deficits were noted in association with 123 of the HPCs, with motor deficit being the most common (occurring in association with 23 [18.7%] of these lesions), followed by cranial nerve deficit (14.6%, n = 18), gait disturbances (11.4%, n = 14), visual acuity deficits (11.4%, n = 14), and convulsions (11.4%, n = 14). Other less common deficits included visual field deficit, sensory deficit, cognitive decline, and hearing loss. Symptoms were reported by 40 patients. The most common symptoms were headache (reported by 18 [45%] patients), lack of energy (reported by 8 [20%]), and tinnitus, dizziness, and neck pain (each reported by 3 [7.5%]).

Tumor Parameters
The median tumor volume at the time of GKRS was 4.9 cm³ (range 0.2–42.4 cm³). Most of the patients (78.9%, n = 71) had WHO Grade II (typical) HPC, with the remainder (21.1%, n = 19) having WHO Grade III (anaplastic) HPC. The most common single lesion location was the cerebral convexity (39.8% of 133 tumors, n = 53), followed by falx (20.3%, n = 27), cerebellopontine angle (12.8%, n = 17), parasellar (12%, n = 16), and tentorial (8.3%, n = 11). Other locations are detailed in Table 2. Intratumoral hemorrhage at the time of GKRS was noted in 4.4% of patients (n = 4).

Radiosurgery Technique
Various Gamma Knife models, including the U, B, C, 4C, or Perfexion, were used depending on the technology available at the time of radiosurgery for the participating centers. The radiosurgical procedure included the application of the Leksell Model G stereotactic frame (Elekta AB) using local anesthetic and additional sedation as needed. Radiosurgical parameters and dose plans were formulated by the treating neurosurgeon in consultation with a medical physicist and a radiation oncologist. The details of stereotactic imaging for radiosurgical planning varied over time, but planning generally included pre- and postcontrast, volumetrically acquired gradient-echo pulse sequences reconstructed into axial and coronal image stacks. When MRI could not be performed due to medical contraindications (e.g., a cardiac pacemaker), a thin-slice (≤ 2.0-mm slice thickness) stereotactic CT scan was performed with and without contrast administration.

The median margin and maximum doses delivered to the tumor margin were 15 Gy (range 2.8–24 Gy) and 32 Gy (range 8–51 Gy), respectively. The median prescription isodose line was 50% (range 30%–97%). For the most part, the dose plans involved a multi-isocentric technique; a median of 3 isocenters (range 1–25) was used. Dose selection relied upon the factors of tumor volume, prior neurological deficits, proximity to critical structures, and history, if any, of prior fractionated radiation therapy. The known WHO grade of confirmed HPCs influenced dose selection as well. Radiosurgical parameters are detailed in Table 2.

Neurosurgical and Radiological Assessment After GKRS
Following GKRS, all patients underwent a clinical evaluation with accompanying imaging follow-up approximately twice a year for the first 2 years, and yearly thereafter. The evaluations included neurological examination and neuroimaging at the patients’ respective treating centers. Symptoms and signs were followed and logged, imag-
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Radiographic evidence of adverse radiation effects (AREs), namely post-GKRS perilesional T2 signal hyperintensity on MRI and relevant clinical correlations, were logged according to the RTOG (Radiation Therapy Oncology Group) scale. Since all participating institutions represent tertiary referral centers, in some cases the patients’ follow-up evaluations were performed by their local physicians. All clinical notes and neuroimaging studies were reviewed by the treating clinicians who performed the GKRS.

Tumor dimensions were assessed in the axial, sagittal, and coronal planes. In follow-up, tumor volume was estimated as \((D_1 \times D_2 \times D_3)/2\), where \(D\) is the maximum diameter of the tumor in a cardinal plane. An increase of more than 10% of the planned treatment volume or tumor occurrence outside the planned treatment volume was deemed tumor progression. Tumor regression was defined as a decrease of the tumor volume by more than 10%. The tumor was deemed stable if its dimensions were within 10% of the volume at the time of GKRS. Local tumor control was defined as reduction or stability of tumor size, categorized as follows: significant shrinkage (volume decrease > 50%), regression (volume decrease of 10%–50%), and stable size (volume change < 10%). An out-of-field progression was defined as another intracranial tumor visible on MRI or CT beyond the planned treatment volume of the known HPC. Extracranial metastases documented by radiographic studies were also recorded as part of this study.

Statistical Analysis

Data are presented as the median and range for continuous variables and as frequency and percentages for categorical variables. Prognostic variables associated with local tumor control (e.g., age, sex, single or multiple lesions, tumor volume, margin radiation dose, maximum radiation dose, pre-SRS management, and tumor grade) were evaluated using Cox univariate and multivariate analysis. Kaplan-Meier curves were plotted for progression-free survival (PFS) from the time of SRS, last follow-up, and failure of treatment, if any.

Prognostic variables related to post-SRS survival (e.g., age, sex, single or multiple lesions, total tumor volume, ex-
tracranial metastasis, margin radiation dose, maximum radiation dose, pre-SRS management, and tumor histology) were also evaluated using Cox univariate and multivariate analysis. Actuarial survival after SRS was analyzed using the Kaplan-Meier method. A p value less than 0.05 was considered to represent statistical significance. All analyses were completed using commercial statistical software (IBM SPSS version 20.0).

**Results**

**Local Intracranial Control and Recurrence**

Outcome parameters are depicted in Table 3. Imaging studies obtained at the most recent post-GKRS follow-up evaluations demonstrated local control in 54.9% of tumors (n = 73) and 62.2% of patients (n = 56) (Fig. 1); 19.5% of the lesions (n = 26) showed a decrease of > 50% of the treatment volume, 18% (n = 24) showed a decrease of 10%–50% of the treatment volume; and 17.3% (n = 23) were considered stable (less than 10% change in volume). Tumor progression and growth (volume increase > 10%) were reported in 45.1% of tumors (n = 60) and 37.8% of patients (n = 34). Actuarial PFS rates from first GKRS at 2, 4, 6, 8, and 10 years were 81.7%, 66.3%, 54.5%, 37.2%, and 25.5%, respectively (Fig. 2).

**Metastasis**

During the study period, distant intracranial progression was reported in 27.8% of patients (n = 25). Extracranial metastatic deposits were identified in 24.4% of patients (n = 22). These extracranial metastases were found in the liver, lung, kidney, bone, bowel, and external auditory canal. The median time to extracranial progression from initial SRS was 21.5 months (range 3–108 months).

**Adverse Radiation Effects**

Radiographic evidence of adverse radiation effects (AREs) (i.e., post-GKRS perilesional T2 signal hyperintensity that is temporary or permanent) was logged according to the RTOG scale. RTOG Grade I was noted in 93.3% of patients (n = 84), whereas RTOG Grades II–IV were noted in 6.7% (n = 6). The median length of time for maximum ARE development was 13 months (range 5–34.5 months).

**Overall Survival After SRS**

As shown in Table 3, during the study period, 32.2% of patients (n = 29) died. In that group of 29 patients, the median time to death was 46 months (range 7–166 months) after initial SRS. Actuarial overall survival (OS) rates from the time of initial SRS at 2, 4, 6, 8, and 10 years were 91.5%, 82.1%, 73.9%, 56.7%, and 53.7%, respectively (Fig. 2).

**Clinical Results**

The median duration of clinical and radiographic follow-up was 59 months (range 1–190 months per lesion and 6–190 months per patient) and 59 months (range 2–183 months per lesion and 6–183 months per patient), respectively. The clinical outcome parameters are depicted in Table 3. At the conclusion of the study period, 67.8% of patients treated in this series (n = 61) remained alive.

**Prognostic Factors Associated With Tumor Control and Overall Survival**

The relative influence of different demographic, tumor,
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and treatment-related factors on tumor control and OS is summarized in Table 4 and Figs. 2–3. With regard to local tumor control (PFS), 2 major factors were shown to be significantly influential both in univariate and multivariate analysis. Treatment-prescribed margin dose higher than 16 Gy (p = 0.037, 95% CI 0.224–0.956 for univariate analysis; p = 0.039, 95% CI 0.194–0.968 for multivariate analysis), and tumor grade (i.e., WHO Grade II vs Grade III; p = 0.006; 95% CI 0.1382–6.616 for univariate analysis; p = 0.011, 95% CI 1.047–5.045 for multivariate analysis). Tumor volume was shown to be influential only in univariate analysis (p = 0.048), but this may be because most tumor volumes treated in this cohort were relatively small due to patient selection (median volume 4.9 cm³, as shown in Table 2).

Reviewing the different parameters that influence OS (Table 4, Figs. 2–3), considering the very long follow-up, only the presence of extracranial metastases was shown to influence OS (p = 0.029, 95% CI 1.103–6.323). WHO grade was not found to be a statistically significant factor (p = 0.057). Other parameters that approached statistical significance included the presence of pre-GKRS resection (p = 0.051) and increasing patient age (p = 0.069).

Repeat GKRS Upon Tumor Recurrence

As expected based upon the behavior of this tumor type and as shown in Tables 3 and 5, recurrence rates were high; 46 patients who presented with recurrence after initial SRS required further treatment, and 32 of these patients elected to undergo repeat SRS. In our cohort, 32 patients underwent 48 repeat SRS procedures for 76 lesions. Reviewing the 76 treated tumors, 17 presented as an in-field recurrence, and 59 tumors were defined as an out-of-field recurrence. The median time between SRS sessions was 34 months (range 4–152 months). The prescribed median margin dose was 14 Gy (range 12–16 Gy). The actuarial PFS was 89% at 2 years, 77% at 4 years, 64% at 6 years, and 54% at 8 years following a second GKRS (Fig. 4). Neither pre-GKRS conventional radiotherapy (EBRT, performed in 38.6% of patients) nor post-GKRS EBRT (performed in 12.2% of patients) was shown to influence PFS or OS.

FIG. 1. Axial Gd-enhanced T1-weighted images obtained from a representative case. A: Preoperative MR image showing an avidly enhancing left tentorial tip/intraventricular mass. Pathological examination demonstrated the lesion to be a WHO Grade II HPC. B: Postoperative, pre-SRS image. SRS was delivered to the residual tumor located at the left intraventricular atrium. A margin dose of 18 Gy was delivered to a treatment volume of 3.3 cm³. C: Follow-up image obtained 13 months after SRS demonstrating local control. D: Follow-up image obtained 129 months after SRS demonstrating continued local control.

FIG. 2. Kaplan-Meier curves for PFS (left) and overall survival (right), with observed cases logged.
TABLE 4. Prognostic factors associated with tumor control and overall survival*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
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<td>1.002–1.063</td>
</tr>
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<td>Sex (M/F)</td>
<td>1.235</td>
<td>0.614–2.483</td>
</tr>
<tr>
<td>Multiple or single tumor(s)</td>
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<td>0.741–3.284</td>
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<tr>
<td>Tumor vol (cm³)</td>
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<td>1.000–1.072</td>
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<td>Margin dose (≤16 vs &gt;16 Gy)</td>
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<td>0.224–0.956</td>
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<td>Max dose (≤32 vs &gt;32 Gy)</td>
<td>0.540</td>
<td>0.268–1.087</td>
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<tr>
<td>Pre-GKRS resection (yes vs no)</td>
<td>1.185</td>
<td>0.909–1.545</td>
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<tr>
<td>Pre-GKRS RT (yes vs no)</td>
<td>1.940</td>
<td>0.974–3.867</td>
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<tr>
<td>Pre-GKRS chemo (yes vs no)</td>
<td>0.048</td>
<td>0.000–688.9</td>
</tr>
<tr>
<td>Tumor grade (II vs III)</td>
<td>3.024</td>
<td>1.382–6.616</td>
</tr>
</tbody>
</table>

Factors associated with overall survival

| Age (yrs) | 1.028 | 0.998–1.058 | 0.069 | 1.030 | 0.997–1.065 | 0.077 |
| Sex (M/F) | 0.566 | 0.250–1.279 | 0.171 | —  | — | — |
| Multiple or single tumor(s) | 1.296 | 0.570–2.948 | 0.536 | —  | — | — |
| Total tumor† vol (cm³) | 1.027 | 0.986–1.069 | 0.199 | —  | — | — |
| Extracranial metastasis | 2.134 | 0.984–4.625 | 0.055 | 2.641 | 1.103–6.323 | 0.029 |
| Pre-GKRS resection (yes vs no) | 1.317 | 0.999–1.737 | 0.051 | 1.018 | 0.687–1.508 | 0.929 |
| Pre-GKRS RT (yes vs no) | 1.857 | 0.847–4.072 | 0.122 | 1.856 | 0.733–4.700 | 0.192 |
| Pre-GKRS chemo (yes vs no) | 2.727 | 0.361–20.61 | 0.331 | —  | — | — |
| Tumor grade (II vs III) | 1.816 | 0.852–3.868 | 0.122 | 1.551 | 0.973–2.804 | 0.057 |

* As determined by Cox regression analysis. Boldface type indicates statistically significant values.
† Tumor control includes regressive and stable tumors.

Discussion

HPCs are rare vascular tumors that arise from mesenchymal cells with pericytic differentiation. Intracranial HPCs are usually well circumscribed, vascular, and aggressive tumors, having a predilection for recurrence and the ability to metastasize. Although these lesions are extremely uncommon, they are exceptionally challenging to treat despite multimodality therapies. Treatment modalities mainly include primary resection and adjuvant EBRT or radiosurgery. Additional modalities used include chemotherapy and embolization. Embolization plays a limited role in HPC management due to the tendency of these tumors to parasitize feeding vessels from both extracranial and intracranial arteries. Many chemotherapeutic agents have been tested, but an effective chemotherapeutic agent for this malignancy has not been reliably demonstrated. The vascular nature of this tumor has sparked some initial studies utilizing bevacizumab, which may offer some future benefit.

Most HPCs can be at least partially resected; however, local recurrence is frequent, occurring in as many as 91% of patients. Histological parameters of proliferation (e.g., MIB-1 index) and malignancy (atypia, necrosis, mitotic figures, etc.) are known to influence prognosis.

Distant metastases have been noted to appear at a mean delay of 63–107 months (range 2–20 years) after initial diagnosis. The incidence of both intracranial and extracranial metastasis increases with time. Intracranial metastasis incidence has been reported as 13%, 33%, and 64% at 5, 10, and 15 years, respectively. The presence of intracranial or extracranial metastases was shown to serve as a negative prognostic factor, significantly shortening survival (p = 0.0312). Most series with long-term follow-up indicate that HPC patients need salvage therapies to prevent tumor recurrence or progression of new tumors.

The Role of GTR and Radiotherapy in HPC Management

Although it is usually the initial treatment for HPCs, resection has been shown to provide poor long-term control of intracranial disease. Resection was reported to carry a 9%–24% risk of operative mortality. In 2010, Rutkowski et al. reviewed a large cohort of HPC cases. In this report, the authors defined several important prognostic factors influencing mortality rates for patients with these tumors. In their cohort of 563 patients, the overall median survival reported was 13 years, with 1-, 5-, 10-, and 20-year survival rates of 95%, 82%, 60%, and 23%, respectively. GTR alone was associated with a median survival of 13 years, whereas STR resulted in a median survival of 9.75 years. Simpson Grade I complete resection has been reported to achieve an improved long-term control rate, and STR has been associated with a high rate of recurrence. Although multiple resections are feasible, the appreciable morbidity associ-
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Ranged with each intervention makes this option unattractive. Resection should intuitively be carried out to the point of maximal safe reduction in tumor volume, yet preserving neurological function.

Melone et al. described in 2014 a single-center experience involving 36 patients with HPC. All patients were treated with initial resection. The median duration of follow-up was impressive at 118 months. The median OS was 84 months, and the actuarial survival rates at 5 and 10 years were 94% and 72%, respectively. GTR was achieved in 70% of patients during initial resection. Postoperative EBRT was administered to 37% and 78% of patients who had GTR and STR, respectively. Patients who underwent STR also received adjuvant treatment with SRS (50%) and proton beam therapy (50%). The duration of both overall and recurrence-free survival was significantly longer for the patients who underwent GTR than for those who un-

<table>
<thead>
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<th>Variable</th>
<th>Value</th>
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<td>Total no of pts who underwent repeated GKRS</td>
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<tr>
<td>Total no. of repeated GKRS procedures</td>
<td>48</td>
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<tr>
<td>Total no. of recurrent targets</td>
<td>76</td>
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<tr>
<td>Time interval between GKRS treatments (months)</td>
<td>34 (4–152)</td>
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<td>Target</td>
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<td>Local tumor recurrence (in-field)</td>
<td>17</td>
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<td>Remote tumor recurrence (out-of-field)</td>
<td>59</td>
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<tr>
<td>Median margin dose in Gy (range)</td>
<td>14 (12–16)</td>
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</table>

FIG. 3. Kaplan-Meier curves showing the influence of WHO grading (A) and margin dose > 16 Gy (C) on PFS and the influence of the presence of extracranial metastases (B) and WHO grading (D) on overall survival. Actuarial numbers are presented in a table form. Refer to text.
The crucial role of attaining GTR when possible was separately shown in other studies as well. The incidence of local recurrence has varied from 26% to 80%, depending on the quality of resection, the length of follow-up, and the delivery of postoperative radiotherapy. Dufour et al. reported a recurrence rate of 88% after surgical removal alone. This rate was reduced to 12.5% with fractionated radiotherapy. Guthrie et al. reported that radiotherapy after the first surgical removal extended the mean time to the first recurrence from 34 to 75 months and extended survival from 62 to 92 months. Postoperative administration of radiotherapy to patients in whom GTR was achieved, however, was not shown to significantly improve OS; rather, SRS and, to a lesser extent, radiotherapy have been shown to improve local tumor control rates after GTR.

**Stereotactic Radiosurgery in HPC Management**

The highly vascular nature of HPCs results in their being avidly enhancing and well demarcated on MRI. These tumors tend to be very sensitive to radiosurgery, of- ten exhibiting rapid and dramatic regression. The steep dose gradient achieved with SRS minimizes unintended radiation to eloquent structures. With radiosurgery, it is possible to deliver a more biologically effective dose to the tumor and minimize the undesired side effects of conventional radiotherapy. A total of 13 studies (including the current paper) have now been published on the use of SRS for recurrent and residual HPC (Table 1). Ecker et al. reported in 2003 a series of 8 patients treated with SRS using a mean margin dose of 20.5 Gy (range 16–24 Gy). The authors reported that 6 (75%) of 8 tumors decreased in size and 2 progressed during a mean follow-up time of 44 months (range 8–77 months). Kano et al. similarly reported that a greater margin dose (> 14 Gy) was significantly associated with better PFS (univariate, p = 0.0023; multivariate, p = 0.0185). The 5-year PFS for patients treated with > 14 Gy was 75.4% compared with 56.3% for those who had received < 14 Gy (p = 0.0023).

Ecker et al. reported in 2003 a series of 38 patients with 22 low-grade and 16 high-grade HPCs who were treated with radiotherapy with or without SRS. High-grade HPCs were shown to recur significantly earlier (3.3 years) than low-grade HPCs (10 years, p = 0.004). The authors concluded that the use of SRS in the treatment of recurrent disease contributed to better survival. Sun and colleagues reported in 2009 a series of 22 patients harboring 58 HPC foci. As with prior reports, there was no correlation between progression of intracranial lesions and development of extracranial metastases. Melone et al. reported in 2014 their experience treating 36 HPCs, with actuarial 5- and 10-year recurrence rates of 50% and 72%, respectively. The authors demonstrated that adjuvant ionizing radiation in any form, including radiosurgery (margin dose 16 Gy), EBRT, and/or proton beam therapy, significantly decreased recurrence rates (p = 0.04) but did not improve OS (p = 0.2). No radiation-induced adverse events, such as necrosis or marked peritumoral edema, were observed.

**Management of Recurrence and Progression**

The aggressive nature of HPCs results in a poor prognosis, in which tumor recurrence is the rule and cure is the exception. Most patients will require more than one treatment modality and procedure to manage their disease. If the patient is deemed as having a low risk of significant surgical morbidity or mortality, repeat resection has been recommended as the first treatment option for recurrent HPC. Alternatively, although results to date are limited and disappointing, the hypervascular nature of HPCs suggests that antiangiogenic strategies might be another feasible therapeutic option for the treatment of recurrent HPCs. This concept is attractive, considering that SRS alone cannot prevent further distant metastases, even when local control is generally achieved. Optimal dosing for the treatment of recurrent HPCs is still a matter of debate.

A higher margin dose appears to achieve a reduction in the rate of local recurrence. The mean margin doses used in previous studies ranged from 13.5 to 17 Gy. Sheehan et al. recommended that a radiation dose of at least 15 Gy should be delivered to the tumor margin for successful local tumor control. Kano et al. reported a significantly better PFS in HPCs treated with a high margin dose (> 14 Gy). Chang et al. applied higher margin doses (mean 20.5 Gy), using LINAC and CyberKnife. Our results support this concept of a higher margin dose (> 16 Gy).
Radiosurgery for intracranial hemangiopericytomas

Gy) for improved local control. Finally, a second GKRS treatment after proven progression yields an added benefit in terms of conferring reasonable PFS (Fig. 4).

Study Limitations
The study is a retrospective one with limitations inherent to its retrospective design. The validity may be limited by patient selection bias inherent to our treatment algorithms. Patients who suffered treatment failure or postradiosurgery complications were followed very closely and had frequent imaging and clinical evaluations and thus might be overrepresented in this cohort. The patients were not all seen at exactly regular follow-up intervals, which made time-to-event statistical analysis less accurate. Treatment was carried out over a long time period and was subject to change in the radiosurgical device, imaging, and software used. Moreover, radiosurgical technology and treatment algorithms have been refined over the study period, and this could have contributed to a bias. Despite these improvements, however, there was no significant difference in the outcome measures over time.

Conclusions
HPCs remain a challenge for neurosurgeons as they exhibit a tendency for aggressive behavior and recurrence. Resection remains the initial treatment option, facilitating histological diagnosis and providing relief of mass effect. Postoperative SRS provides an effective and safe adjuvant management option for patients with recurrent or residual HPCs. SRS (at a margin dose > 16 Gy) is effective in increasing local tumor control and the time to progression. Since SRS is a focal treatment, it does not eliminate the possibility of regional or distant metastases, and metastasis remains a source of significant morbidity and mortality for these patients. Close follow-up and repeat radiosurgery can be used in cases of recurrence or distant intracranial disease progression. Given the rarity of this tumor type, the best available data are likely derived from retrospective analysis of a multicenter database as presented in this study or a prospective registry.

Acknowledgments
The authors wish to acknowledge the assistance of Lisa Baxendale, the clinical coordinator for the IGKRF.

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Disclosures
Dr. Lunsford reports a shareholder and consultant relationship with Elekta AB. Dr. Grills reports being on the Board of Directors of and having an ownership interest in Greater Michigan Gamma Knife.

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