Clinical Study

Hemangiopericytoma: Radical resection remains the cornerstone of therapy

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ABSTRACT

Hemangiopericytomas (HPC) are mesenchymal tumors with a propensity towards chronicity and metastasis. This study aimed to reflect a single institution experience with both World Health Organization (WHO) grade II and III HPC. Pathology records from the years 1990–2013 at the University of Washington were searched to identify tumors unequivocally classified as HPC. Electronic chart review was then utilized to collect pertinent patient data. Of the WHO grade II HPC, there were four men and two women (average age 52 years) while the grade III HPC group had eight men and two women (average age 51 years). Sixty-six percent of WHO grade II tumors were located in the middle or posterior fossa as compared to none of the grade III tumors. Survival analysis revealed a significant survival benefit for patients who underwent complete resection (223 months) versus those with subtotal resection (138 months, \( p < 0.05 \)). Factors such as age, sex, the use of up-front radiation, and whether the patient had a recurrence did not show statistical significance related to overall survival or progression free survival. Radiation in the form of external beam radiotherapy given at the time of the first recurrence did trend towards improved progression free survival (56 months) compared to those patients who were not radiated (22 months, \( p = 0.09 \)). All patients with radical resection went on to never have a recurrence. Our results indicate that HPC are tumors with limited response to radiation and best treated with aggressive resection. Future studies will determine whether molecular-based therapies may provide added adjuvant benefit.

1. Introduction

Hemangiopericytomas (HPC) are rare tumors, thought to comprise 2–3% of all primary meningeal tumors and 1% of all intracranial tumors [1–5]. Histologically, HPC is believed to arise from Zimmerman pericytes, which are contractile spindle cells surrounding capillaries in any part of the human body [1,2,6]. These tumors were previously thought to be angioblastic variants of meningioma; however in 1993 the World Health Organization (WHO) recognized these tumors as distinct clinicopathological entities on the basis of their histologic characteristics and their tendency to recur and metastasize extraneurally [1,7–13]. Academic progress on these entities has been halting, mainly because of their rarity and potential chronicity [1–12,14–40].

Recent literature has advocated gross total resection with or without postoperative external beam radiotherapy (EBRT) on the basis of one large series [1] and another meta-analysis [2]. As long term survival is quite possible with these tumors, particularly in patients with gross total resection, the decision to radiate is critically important given that many patients are relatively young at the time of diagnosis. The purpose of this study was to evaluate the efficacy of gross total resection with radiation in a single institution series of 16 patients with a mean follow-up of 91 months.

2. Methods

The study involved 16 patients with primary HPC of the central nervous system who were treated at the University of Washington between 1990 and 2013. Patients were identified from histopathological records. Medical records were analyzed retrospectively to collect demographic, treatment, and outcome data.

The extent of tumor resection was established from operative notes and imaging review. Extent of tumor resection was defined using a modified Simpson grade with grade 1 delineating radical tumor resection with dural margins and bony drilling while grade 2 conferred subtotal resection status. Pathology reports were reviewed to confirm diagnosis and determine if the tumor was low or high grade on the basis of WHO criteria. With regards to radiation, modality (such as EBRT or Gamma Knife [Elekta AB,
Stockholm, Sweden]) was recorded along with treatment dose. No patients received chemotherapy.

2.1. Follow-up data

Recurrence was defined as local tumor growth as identified on serial imaging. Local recurrences were treated with revision surgery followed by radiation when radical excision was not possible. Adjuvant radiation was performed if significant tumor bulk remained after the first operation. The modified Rankin scale (mRS) was used to assess quality of life at last follow-up.

2.2. Statistical analysis

Clinical data related to survival analysis was analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) using the Kaplan–Meier method [41]. Univariate comparison of parameters was performed using log-rank analysis. Multivariate analyses were not performed given the small sample size of the study population thus precluding meaningful results.

3. Results

Sixteen patients underwent microsurgical resection for HPC between 1990 and 2013. The minimum number of operations was one and a maximum nine. There were three women (25%) and 13 men (75%) with a mean age at diagnosis of 51 years (range 24–74 years). The mean follow-up was 91 months (range 0.16–246 months). No patient was lost to follow-up. The mortality rate was 25%. The 5 year survivor rate was 70%. Only one patient developed extraneural metastases. The mRS score at last follow-up indicated a score of 0 (indicating independent symptom free life) for nine patients, a score of 6 (indicating death) for four patients, and a score of 3 (indicating mild disability but independent) for one patient. Twenty-seven percent of patients received up-front radiation mostly with EBRT (only one patient received up-front stereotactic radiosurgery).

3.1. Recurrence rate

Six patients (37.5%) developed local recurrence at an average of 59 months (range 9–117 months). Four patients suffered from a minimum of four recurrences and a maximum of nine. The average follow-up for those with recurrences was 164 months. Only one patient who recurred died. The mortality rate was 25%. The 5 year survivor rate was 70%. Only one patient developed extraneural metastases. The mRS score at last follow-up indicated a score of 0 (indicating independent symptom free life) for nine patients, a score of 6 (indicating death) for four patients, and a score of 3 (indicating mild disability but independent) for one patient. Twenty-seven percent of patients received up-front radiation mostly with EBRT (only one patient received up-front stereotactic radiosurgery).

3.2. Factors affecting prognosis and recurrence

Univariate statistics were used to evaluate demographic and treatment data including extent of resection, up-front radiation, the use of multiple radiation treatments, age less than 40, sex, and the presence of recurrence with regards to mortality and tumor recurrence (Table 1, 2). Mortality was observed to be increased in tumors exhibiting high grade (40%) features compared to lower grade tumors, but not significantly so (0%, p = 0.15). Additionally, radical resection imparted a significant survival benefit with a mortality of 10% in completely resected tumors and 50% in subtotally resected tumors (p = 0.04, Fig. 1). Age, sex, and the use of radiation either up-front or repeated as salvage therapy did not impart a survival benefit (Fig. 2, 3).

With regards to progression, none of the studied factors seemed to significantly affect whether or not a tumor recurred. Notably, of the three tumors that recurred in the subtotally resected group, all three were completely removed at the time of recurrence with no further recurrence following the second operation.

### Table 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mortality</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>HPC grade</td>
<td>Low 0%</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>High 40% ± 16%</td>
<td></td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Grade 1 10% ± 9%</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Grade 2 50% ± 22%</td>
<td></td>
</tr>
<tr>
<td>Up-front radiation</td>
<td>None 22% ± 14%</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>EBRT 29% ± 18%</td>
<td></td>
</tr>
<tr>
<td>Multiple radiation</td>
<td>Yes 16% ± 15%</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>No 30% ± 15%</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 40 years</td>
<td>Yes 25% ± 24%</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>No 25% ± 13%</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>Yes 14% ± 13%</td>
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</tr>
<tr>
<td></td>
<td>No 33% ± 16%</td>
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**BBRT = external beam radiotherapy, HPC = hemangiopericytoma. Data are presented as mean ± standard error of the mean.**

### Table 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>Progression</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC grade</td>
<td>Low 16% ± 17%</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>High 50% ± 16%</td>
<td></td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Grade 1 30% ± 15%</td>
<td>0.22</td>
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<tr>
<td></td>
<td>Grade 2 50% ± 22%</td>
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<tr>
<td>Up-front radiation</td>
<td>Yes 29% ± 0.18%</td>
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<td></td>
<td>No 44% ± 17%</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 40 years</td>
<td>Yes 75% ± 25%</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>No 25% ± 13%</td>
<td></td>
</tr>
</tbody>
</table>

**HPC = hemangiopericytoma. Data are presented as mean ± standard error of the mean.**

![Fig. 1. Kaplan–Meier survival curve showing radical resection imparts significantly increased survival (median 6708 days) compared to subtotal resection (median 4147 days, p = 0.04). Notably, there were six high grade tumors in the total resection group thus suggesting extent of resection affects overall survival independent of tumor grade. Cum = cumulative.](image)

4. Discussion

HPC are rare and potentially aggressive lesions. Recent case series and meta-analyses have revived the debate regarding the role of radiation in the treatment of these lesions [1,2]. We present a series of 16 patients with central nervous system HPC treated at a single center. The most notable findings included the lack of effect of...
Extent of resection has increasingly been shown to correlate with improved long term and recurrence free survival. In clinical series ranging in samples sizes from 17 to 40, overall survival ranged from 59 to 232 months (mean of 57 months in current study among those who died [1,3,4,25–27,37,38,40]. In these same studies, one-third to one-half of patients underwent EBRT and 50–75% of patients underwent gross total resection (43% and 63%, respectively, in the current series). Moreover a recent meta-analysis demonstrated a 10 year survival rate of 69% in those patients undergoing gross total resection compared to 44% in those who underwent subtotal resection [2]. Our study further validates the claim that these lesions should be treated by physicians who can safely achieve radical resection; this is of special import given the propensity of these lesions to involve difficult-to-access locations in the skull base and/or along venous sinuses.

With regards to radiation, our study does not support the use of radiation as an adjunct to gross total resection. Certainly, a recent meta-analysis of over 250 patients demonstrated that gross total resection is significantly better than subtotal resection, even when subtotal resection is paired with adjuvant radiation therapy [2]. Moreover, the addition of adjuvant radiotherapy to gross total resection did not improve overall survival. On the other hand, the radiation literature regarding fractionated radiotherapy has sometimes shown benefit in preventing tumor progression [3–5,11,15,36] but meta-analyses indicate very little gain from radiation and perhaps even harm in doses over 50 Gy [2]. In addition, studies from the stereotactic radiosurgery literature report local control rates of approximately 50% (rates range from 50–80% in the literature [7,20,21,23–25,30]) in residual or recurrent tumors though the 5 year progression free survival was only 28.7% (improved in lower grade patients and those who received a higher marginal dose >14 Gy) [33,34]. In our series, we also examined whether EBRT given at the time of first recurrence improved progression free survival which did reveal a trend towards improvement in the radiated group (Fig. 2). Therefore, the use of radiation with regards to these lesions should be carefully examined with respect to each individual patient.

The low frequency of HPC makes its study particularly challenging. Given the small size of even the largest case series, conclusions that can be drawn regarding prognostication and factors affecting treatment outcome are limited. Increasingly, however, it has become most apparent that radical resection offers the best chance of long term tumor control, regardless of tumor grade. Given that the a priori diagnosis of HPC is often not possible, central nervous system lesions that may be HPC should be resected as radically as possible, including dural margins, bony resection, and even resection of venous sinus disease if feasible.

Because of the rarity of HPC and potential long term chronicity with radical treatment, no single institution is likely to have a large enough series to answer all the relevant questions about the behavior and treatment response of HPC. Future studies should therefore be directed at studying the basic biology of these tumors, in an effort to determine molecular characteristics and potential avenues of drug therapy for sensitive tumors. For example, given the well-known vascularity of these tumors, it is possible that anti-angiogenic agents such as bevacizumab may be useful (this has been attempted in combination with temozolomide in a small series of patients with metastatic HPC with marginal results [35]). Certainly salvage chemotherapeutic approaches, where published, have shown only marginal efficacy thus requiring more robust clinical and basic research to find better salvage treatment options [29]. Recent reports identifying the NAB2-STAT6 fusion protein in both central nervous system HPC and solitary fibrous tumor (of which HPC is thought to be a closely related variant), identifiable by STAT6 immunostaining are encouraging directions in this line of work [42,43].
5. Study limitations

Obvious concerns arise when performing retrospective analyses of small clinical populations, particularly when analyses require separation of the entire cohort into smaller groups for the purposes of univariate analyses. As such, our study has purposefully restricted the number of study variables to analyze and avoided multivariate analysis altogether. As such, the small sample size restricts the ability to make concrete inferences. Nevertheless, given the rarity of this tumor, and the significance of including radiation within the treatment armamentarium, this study corroborates other studies suggesting the lack of benefit with regards to radiation.

6. Conclusions

HPC continues to reflect a challenging clinicopathological entity whose optimal treatment remains to be defined. Certainly, gross total resection provides the most robust predictor of long term outcome but given the frequent challenge of achieving this surgical goal, other treatment modalities need to be refined. Recent studies that molecularly relate central nervous system HPC with solitary fibrous tumor may open new doors of treatment from solitary fibrous tumor oncology experience. It is these types of studies exploring the molecular nature of these tumors that will ultimately lead to durable non-surgically based adjuvant treatments.

Conflicts of interest/disclosure

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References