Objective: To provide benchmarks for further studies of solitary fibrous tumor/hemangiopericytoma (SFT/HPC) of the central nervous system (CNS), we investigated the association of baseline demographic, clinico-pathologic, and treatment factors with outcomes in those treated at our center.

Methods: We conducted a retrospective, cohort analysis of patients treated for SFT/HPC at the University of Washington 1990–2020. Kaplan-Meier and univariable Cox analyses assessed relationships between baseline variables and local or global CNS recurrence, extraneural recurrence, progression-free survival (PFS) and overall survival (OS).

Results: Among 34 eligible patients, median duration of follow-up was 79 months (range 13–318 months). Local and global CNS recurrence occurred at a median of 81 m (95% CI 48–151) and 81 m (95% CI 47–112), respectively. Extraneural metastases occurred at a median 248 m (95% CI 180-Not Reached) and only in grade 3 tumors. Median PFS and OS were 76 months (95% CI: 47–109 months) and 210 months (95% CI 131–306 months), respectively. Univariable Cox analyses showed that age at diagnosis was associated with local (p = 0.01) and global CNS relapse (p = 0.01), and PFS (p = 0.03). Gross total resection was associated with decreased local or global CNS relapse (p = 0.02) and improved PFS (p = 0.03); peri-operative radiation was associated with decreased local CNS relapse (p = 0.02).

Conclusion: Following microsurgical resection of SFT/HPC, CNS relapse is common and associated with age, extent of resection, and adjuvant radiation. Extraneural relapse occurs in some patients. Delayed time-to-initial relapse justifies prolonged surveillance, but optimal approaches have not been defined.

Keywords: solitary fibrous tumor, hemangiopericytoma, radiotherapy, embolization, adjuvant

Introduction
First described in 1942 by Stout and Murray, solitary fibrous tumor (SFT)/hemangiopericytoma (HPC) of the central nervous system (CNS) represents about 2.5% of meningeal-based tumors and less than 1% of intracranial tumors.1,2 CNS SFT/HPC arises from the pericytes of the meningeal capillaries of the neuraxial dura. Patients present at a mean age of approximately 44 years. SFT/HPC may present with clinical and imaging findings similar to meningiomas, but, unlike most meningiomas, they are characterized by high rates of local CNS recurrence and the potential for extracranial metastasis.2,3
Until 2013, SFT and HPC were considered to be distinct entities, with HPC being viewed as a more aggressive entity. However, they were confirmed to share a common chromosomal inversion at the 12q13 locus, yielding a fusion protein consisting of the NGFR-A-binding protein 2 (NAB2) fused to the signal transducer and activator of transcription 6 (STAT6) protein. Presently, these tumors are classified as SFT, with about 10% representing a more clinically aggressive subtype that displays a propensity for local recurrence and distant dissemination, formerly termed HPC. We use the combined term SFT/HPC to acknowledge the terminology used in older literature.

In addition to their rarity, SFT/HPC of the CNS is associated with prolonged survival. These factors make prospective trials challenging or impossible to conduct. Virtually all data to guide treatment recommendations come from case reports, small case series and derivative analyses, such as systematic reviews.

Surgery is the mainstay of SFT/HPC treatment. Studies vary with respect to the benefit conferred by surgery. Some studies suggest improved relapse-free survival (RFS) for those with gross total resection (GTR), but no overall survival (OS) benefit. In others, GTR is associated with improved OS. Peri-operative radiation therapy (RT) is another frequently employed modality. While Bastin and Mehta in 1992 argued for both local control and OS benefits from peri-operative RT, more recent analyses have yielded mixed results. Some studies suggest a local control benefit, without improved OS. Others do not identify benefit in either regard. The systematic review of Ghose et al found that GTR and peri-operative RT were associated with improved OS.

Clinical endpoints reported in studies of SFT/HPC are also varied. While OS has a clear interpretation, other endpoints have a less unitary definition. For example, progression-free survival (PFS) and RFS are composite endpoints, combining OS with other markers of disease progression/relapse (local control, relapse in the distant neuraxis, extraneural/extra-cranial relapse). Expected outcomes for these varied endpoints have not been completely defined, hindering progress in the design and execution of research studies.

Here, we report a single-institution experience treating intracranial SFT/HPC in 34 patients. This includes updated data from 13 patients previously reported. We analyze a variety of outcomes with respect to baseline demographic, clinico-pathologic and treatment factors. We seek to identify factors associated with treatment outcomes, in order to provide benchmarks for interpretation of retrospective data, and to inform the designs of future clinical trials.

Methods
Patient Selection and Data Collection
This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for cohort studies. This retrospective analysis uses data from patients treated at the University of Washington hospital system between January 1990 and December 2020. Specimen and data collection were reviewed and approved by the University of Washington Institutional Review Board and Human Subjects Division (IRB STUDY00002162 and IRB STUDY00010743). Written informed consent was obtained from all patients who were alive and contactable. For those from whom consent could not be obtained (for example, due to patient death or inability to contact), the study was conducted under a waiver of consent, as approved. Studies were carried out following relevant guidelines and regulations, including adherence to the principles defined in the Declaration of Helsinki.

Clinical review was performed using the electronic medical record system and University of Washington’s neuropathology database, reviewed from January 1990 to October 2020, for tumor specimens indicative of potential SFT/HPC (n = 150; Figure 1). Duplicate patient records were consolidated. Neuropathology reports issued by board-certified neuropathologists, operative reports, and follow-up documentation were reviewed for confirmation of SFT/HPC diagnosis and microsurgical resection. Patients with an extra-cranial primary site, those undergoing only biopsy of the primary tumor (versus therapeutic surgical resection), and those with less than 12 months of follow-up were excluded. Those in the latter group were excluded as being unreflective of the long natural history of SFT/HPC, and consisted of patients who received surgical treatment at the University of Washington, but did not have ongoing follow-up information available to assess outcomes.

Pathologic information was derived from review of the neuropathology reports. Demographic data, including sex and race, were obtained from chart review. Age was determined at the time of initial diagnosis. Era of treatment was
determined from the median year of treatment, with the dataset being dichotomized at the median year (1990–2008 and 2009–2020). Imaging characteristics, including tumor location and size, were determined from review of pre-operative imaging. Tumor size was calculated using the ellipsoid formula \( \frac{\pi}{6} \times \text{anterior-posterior} \times \text{cranial-caudal} \times \text{medial-lateral} \). Because of the large timespan encompassed by the patients in the study, actual imaging data were not available on 12/34 eligible patients. Thus, analyses of the effect of tumor volume were based only on data from 22 patients for whom sufficient imaging results were available.

Operative details were abstracted from the treating surgeon’s operative report. Extent of resection was determined by review of post-operative imaging and surgical records. GTR was defined as the surgeon’s description of complete surgical removal of tumor and the absence of residual enhancement on postoperative MRI scans obtained within 48 hours of surgery. This definition is consistent with that of others. Local progression/recurrence was defined as a minimum of 0.5 cm of tumor growth on postoperative MRI scans. Distant CNS metastases were defined as tumor recurrences greater than 1 cm from the original resection cavity and within the CNS, including the spinal neuraxis. Extraneural/extracranial metastases were determined from review of radiology reports. Survival status was determined by review of clinical documentation and direct contact with the patient or their family. Receipt of pre-operative embolization status was determined from clinical notes. Patients were only considered to have had such a procedure prior to the initial surgical procedure if a procedure note was documented, or the clinical or operative notes indicated that such an antecedent procedure had been performed. Patients in whom such a procedure was explicitly not undertaken prior to the first surgery, or for whom no such procedure was documented (classified as “unknown” in Table 1), were classified as not having received such a procedure.

**Statistical Analyses**

Data were summarized using descriptive statistics. Where appropriate, median, range, mean, and standard deviation (sd) were calculated. The primary endpoints of interest were local recurrence at the original treatment site, metastasis at any...
For local recurrence, CNS metastasis, and extraneural metastasis, both loss-to-follow-up and death without recurrence/metastasis were censored in survival analyses. These outcomes were analyzed using Kaplan–Meier analyses with the log-rank test to assess for statistical significance and by

| Characteristic                      | Parameter          |
|------------------------------------|--------------------|
| Sex                                | Female 17 (50%)    |
|                                    | Male 17 (50%)      |
| Age at first surgery (years)       | Median 44          |
|                                    | Range 20–80        |
| Race                               | White 30 (88%)     |
|                                    | Black 1 (3%)       |
|                                    | Other/Unknown 3 (9%) |
| Era of treatment                   | 1990–2008 17 (50%) |
|                                    | 2009–2020 17 (50%) |
| Tumor grade                        | 1 3 (9%)           |
|                                    | 2 10 (29%)         |
|                                    | 3 21 (62%)         |
| Tumor volume (cm$^3$; n=22)        | Median 19.5        |
|                                    | Mean (Standard Deviation) 38.9 (46.6) |
|                                    | Range 2.5–134.9    |
| Tumor location                     | Supratentorial 25 (74%) |
|                                    | Infratentorial 9 (26%) |
| Gross total resection              | Yes 23 (68%)       |
|                                    | No 11 (32%)        |
| Perioperative radiation therapy    | Neoadjuvant 3 (9%) |
|                                    | Adjuvant 22 (65%)  |
|                                    | Any 23 (68%)       |
| Preoperative Embolization           | Yes 10 (29%)       |
|                                    | No 13 (38%)        |
|                                    | Unknown 11 (32%)   |
| Duration of follow-up (months)     | Median 79          |
|                                    | Range 13–318       |
| Deaths observed                    | Yes 10 (29%)       |
|                                    | No 24 (71%)        |
univariable Cox proportional hazards models. For all outcomes, the timespan encompassed in the analyses began with the time of initial diagnosis of SFT/HPC. Because of the inclusion of patients receiving both GTR and subtotal resection, PFS is considered synonymous with RFS.

All statistical comparisons were performed using either SPSS statistics software for Mac, Version 27 (IBM) or Stata version 15.1 (StataCorp, College Station, Texas, USA). A p-value ≤0.05 was defined as the threshold for statistical significance.

**Results**

**Baseline Characteristics**

Between January 1990 and October 2020, 34 patients were identified for study (Figure 1). The baseline characteristics are summarized in Table 1. There were 17 women (50%) and 17 men (50%), with a mean age of 44 years (range: 20–80 years). The majority were Caucasian (88%). Seventeen patients (50%) were treated in the 1990–2008 era; the remaining patients were treated in the 2009–2020 era. The age distribution at time of first surgery was different in these two eras (1990–2008: mean 42.2 y, sd=11.1; 2009–2020: mean 54.4 y, sd=17.3; two-sided t-test assuming unequal variances, p = 0.02). There was no difference with respect to treatment era in the remaining demographic, clinico-pathologic or treatment variables.

A total of 3 (9%), 10 (29%), and 21 (62%) patients were diagnosed with grade 1, grade 2, and grade 3 SFT/HPC, respectively. The majority of tumors were supratentorial (74%). Imaging analysis was available in only 22 cases. Based on these 22 cases, the average tumor volume was 39 cm$^3$. All subsequent analyses of the association between tumor volume and outcomes were limited to this subset of 22 patients. Ten patients (29%) underwent pre-operative embolization. The entire cohort underwent 72 cranial operations (mean: 2.1 operations/patient, range: 1–8). GTR of the primary tumor was achieved in 23 patients (68%). Twenty-three patients (68%) received perioperative radiotherapy, of whom 1 (3%) received only neoadjuvant therapy, 20 (59%) received adjuvant therapy, and 2 (6%) received both neoadjuvant and adjuvant therapy.

The median length of follow-up from the date of diagnosis was 79 months (range 13–318 months). Eighteen patients (53%) experienced local CNS recurrence, while 21 (62%) experienced any CNS recurrence/metastasis, whether local at initial resection site or distant within the CNS and neuraxis. Eight patients (24%) developed extraneural metastases. There were 23 (68%) patients who experienced an event defining PFS (either progression at any site or death) and 10 (29%) patients died during the follow-up period, qualifying as an event defining OS.

**Central Nervous System Recurrence**

Local recurrence and metastasis at any site within the CNS were evaluated. Median time to local CNS recurrence was 81 months (95% CI 48–151 months) (Figure 2A; Supplemental Materials Table 1). Older age at the time of initial diagnosis was associated with increased risk of local CNS recurrence (Hazard Ratio/HR 1.05, 95% Confidence Interval/CI 1.01–1.09; p = 0.01), while treatment with perioperative radiotherapy was associated with decreased risk of local CNS recurrence (HR 0.30, 95% CI 0.11–0.82; p = 0.02) (Table 2). Neither extent of resection nor preoperative embolization was statistically associated with local CNS recurrence.

Median time to recurrence at any CNS site (local or distant) was 81 months (95% CI: 47–112 months) (Figure 2B; Supplemental Materials Table 1). Older age at diagnosis (HR 1.05, 95% CI: 1.01–1.09; p = 0.001), earlier treatment era (1990–2008) (HR 4.37, 95% CI: 1.27–15.1; p = 0.02), and GTR (HR 0.32, 95% CI: 0.12–0.83; p = 0.02) were associated with decreased rates of local or distant CNS recurrence/metastasis (Table 2). When any CNS recurrence/metastasis was assessed with respect to age at time of first surgery (categorized as above or below the median age = 44), stratifying for treatment era, age remained statistically significant (log rank $\chi^2$ 12.50, p = 0.0004). In contrast, treatment era was not associated with any CNS recurrence/metastasis, after stratifying for age at first surgery (log rank $\chi^2$ 1.72, p = 0.19). Neither preoperative embolization, treatment with perioperative radiotherapy, nor any other variable was associated with development of global CNS recurrence/metastasis.
Extraneural Metastasis

Eight patients developed extraneural metastatic disease: 4 (50%) developed lung metastases, 4 (50%) developed liver metastases, and 3 (38%) developed bone metastases. Median time-to-extraneural metastasis was 248 months (95% CI: 180 months-Not Reached) (Figure 2C; Supplemental Materials Table 1). As all patients who developed extraneural metastases possessed histologic grade 3 tumors, no HR could be calculated. Instead, the log-rank test was used to

Figure 2 Kaplan-Meier analyses with respect to various endpoints for solitary fibrous tumor/hemangiopericytoma. Shaded area indicates 95% confidence interval. (A) Local central nervous system (CNS) relapse; (B) any/global CNS relapse; (C) extraneural relapse; (D) progression-free survival; (E) overall survival.
Table 2 Univariable Cox Regression with Respect to Survival Outcomes

| Characteristic* | Local CNS Recurrence | Any CNS Recurrence/ Metastasis | Extraneural Metastasis | Progression-Free Survival | Overall Survival |
|-----------------|----------------------|--------------------------------|------------------------|--------------------------|-----------------|
|                 | HR (95% CI)          | p                               | HR (95% CI)            | p                        | HR (95% CI)    | p               |
| Sex             |                      |                                 |                        |                          |                 |                 |
| Male            | Referent             |                                 | Referent               |                          | Referent       |                 |
| Female          | 0.78 (0.29–2.11)     | 0.63                            | 1.03 (0.42–2.55)       | 0.94                     | 1.02 (0.43–2.40)| 0.97            |
|                 |                      |                                 | Referent               |                          | Referent       |                 |
| Age at first surgery# | 1.05 (1.01–1.09) | 0.01                            | 1.05 (1.01–1.09)       | 0.01                     | 1.00 (0.95–1.06)| 0.99            |
| Era of treatment |                      |                                 |                        |                          |                   |                 |
| 1990–2008       | Referent             |                                 | Referent               |                          | Referent       |                 |
| 2009–2020       | 3.47 (1.94–12.8)     | 0.02                            | 3.47 (1.94–12.8)       | 0.02                     | 3.09 (0.48–19.8)| 0.23            |
| Tumor grade     |                      |                                 |                        |                          |                   |                 |
| 1/2             | Referent             |                                 | Referent               |                          | Referent       |                 |
| 3               | 2.24 (0.71–7.05)     | 0.17                            | 2.24 (0.71–7.05)       | 0.17                     | 2.22 (1.94–3.58)| 0.07*           |
| Tumor volume (n=22) | 1.00 (0.99–1.02) | 0.65                            | 1.00 (0.98–1.01)       | 0.65                     | 1.02 (0.99–1.04)| 0.17            |
| Tumor location  |                      |                                 |                        |                          |                   |                 |
| Infratentorial  | Referent             |                                 | Referent               |                          | Referent       |                 |
| Supratentorial  | 0.82 (0.29–2.36)     | 0.72                            | 0.75 (0.29–1.97)       | 0.56                     | 0.63 (0.11–3.79)| 0.62            |
| Gross tumor resection |          |                                 |                        |                          |                   |                 |
| No              | Referent             |                                 | Referent               |                          | Referent       |                 |
| Yes             | 0.40 (0.15–1.04)     | 0.06                            | 0.32 (0.12–0.83)       | 0.02                     | 0.99 (0.23–4.19)| 0.98            |
| Perioperative RT |                      |                                 |                        |                          |                   |                 |
| No              | Referent             |                                 | Referent               |                          | Referent       |                 |
| Yes             | 0.30 (0.11–0.82)     | 0.02                            | 0.48 (0.19–1.18)       | 0.11                     | 1.64 (0.37–7.32)| 0.52            |
| Preoperative Embolization |          |                                 |                        |                          |                   |                 |
| No/Unknown      | Referent             |                                 | Referent               |                          | Referent       |                 |
| Yes             | 0.41 (0.09–1.80)     | 0.24                            | 0.70 (0.20–2.45)       | 0.58                     | 0.76 (0.08–6.81)| 0.81            |
| Notes: Race not assessed due to inadequate number of non-white cases. *Calculations based on all 34 cases, with the exception of tumor volume, which included only 22 cases with data. #Per year of age, referenced to 20 years of age. %Hazard ratio could not be calculated; comparison calculated by log-rank test. Abbreviations: CI, confidence interval; HR, hazard ratio; NC, not calculable, due to all patients with extracranial disease having grade 3 lesions; p, p-value; RT, radiation therapy.
compare those with grade 3 tumors versus those with either grade 1 or 2 tumors (log-rank $\chi^2$ 3.26, $p = 0.07$), and suggested a trend towards higher rates of extraneural metastasis with grade 3 tumors. None of the remaining demographic, clinico-pathologic, or treatment variables was significantly associated with development of extraneural metastases (Table 2). Only one patient (3%) received systemic therapy, and therefore no conclusions could be drawn about the impact of such therapy on the course of metastatic disease.

**Progression-Free Survival and Overall Survival**

Median PFS was 76 months (95% CI: 47–109 months) (Figure 2D; Supplemental Materials Table 1). Age at first surgery (HR 1.04, 95% CI: 1.00–1.08; $p = 0.03$) and era of treatment (HR 4.85, 95% CI 1.46–16.1; $p = 0.01$) were both statistically significant in univariable Cox analyses (Table 2). However, when PFS was assessed with respect to age at time of first surgery (categorized at the median age), stratifying for treatment era, age remained statistically significant (log-rank $\chi^2$ 9.18, $p = 0.002$). In contrast, treatment era was not associated with PFS, after stratifying for age at first surgery (log-rank $\chi^2$ 2.96, $p = 0.09$). Extent of resection (GTR) was associated with improved PFS (HR 0.36, 95% CI 0.15–0.91; $p = 0.03$). None of the other variables were associated with PFS, including treatment with perioperative radiation therapy and preoperative embolization.

Median OS was 210 months (95% CI 131–306 months) (Figure 2E; Supplemental Materials Table 1). None of the assessed demographic, clinico-pathologic, and treatment variables were associated with OS (Table 2).

**Discussion**

Despite the rarity of CNS SFT/HPC, this condition can present a significant challenge to both the treating surgeon and oncology teams. These tumors can recur locally, or metastasize to other CNS and extra-cranial sites. Information regarding patient outcomes to help guide treatment, surveillance, patient education, and the design of clinical investigations is limited, which motivated our study.

As noted earlier, SFT and HPC were first included in the 2002 World Health Organization (WHO) classification of CNS tumors and their grading remained unchanged until the 2016 revision. SFTs were considered benign grade 1 lesions and distinct from the more aggressive HPCs, which were considered grade 2 or grade 3. By 2013, both SFTs and HPCs were found to share a common fusion of the NAB2 and STAT6 genes, and nuclear overexpression of STAT6. These specific markers led SFTs and HPCs to be unified into a single entity and renamed SFT/HPC. In the 2021 WHO classification of CNS tumors, these tumors are referred to simply as SFT, under the category of mesenchymal, non-meningotheial tumors. The HPC term has become obsolete. The three-tier WHO grading system distinguishes the differing clinical behavior, instead of the use of variable terms.

Our data describe outcomes observed in patients undergoing microsurgical resection of a primary CNS SFT/HPC. The outcomes for study reflected challenges with local and global CNS disease control (local CNS recurrence, any CNS metastasis), extraneural disease control, and survival (PFS, OS). Critically, all participants must have been able to undergo therapeutic surgical resection of the primary tumor, representing the majority of SFT/HPC patients. Our results do not apply to the minority of patients who do not undergo surgical management, either for technical reasons, performance status, co-morbidities, or other reasons. Our study reflected this reality, with only 2 out of 47 potentially eligible patients not undergoing attempted resection. Such patients may be able to receive treatment with radiotherapy or systemic therapy. We would anticipate that outcomes in the absence of surgery would be inferior, since surgical intervention is frequently indicated due to significant neurological deterioration.

To date, surgical resection remains the cornerstone of therapy for SFT/HPC, both for alleviation of mass effect and oncologic care. Factors associated with extent of resection can include tumor location (skull base versus convexity), association and invasion of dural sinuses, and surgeon experience, amongst others. We found that extent of resection (GTR) was associated with improved PFS, though not OS. Giordan et al reported that extent of resection was associated with local recurrence and a significant factor for decreasing the risk of development of metastases. Similarly, a second systematic review of 523 patients reported that GTR was associated with a mean survival of 157 months, versus 110 months for patients undergoing subtotal resection.
Recurrence within the CNS, particularly at the site of initial diagnosis, was the primary mode of treatment failure, with a median time to local recurrence or any CNS recurrence/metastasis of 81 months (95% CI 47–112 m). These findings are consistent with the results of others, taking into account the relatively small number of patients in individual series and consequent wide confidence intervals. Increasing age at the time of diagnosis was associated with increasing risk of both local recurrence and global CNS recurrence/metastasis, and of decreased PFS. Considering all three endpoints (local CNS recurrence nested within any CNS recurrence/metastasis nested within PFS), both GTR and treatment with peri-operative radiotherapy were associated with decreased global CNS recurrence/metastasis and PFS, and local CNS recurrence, respectively.

Peri-operative radiotherapy is associated in some studies with decreased local recurrence at the primary site of disease, although not all studies identified this benefit. The small size of most primary studies, limiting the statistical power to detect a benefit, and varied RT treatment protocols may explain differences in inter-study conclusions. Our results support the potential benefit of peri-operative RT. The systematic review of Ghose et al also suggests an OS benefit of peri-operative RT, although the conclusions of such an analysis must be tempered by the great variability in the underlying reports supporting such a systematic review. In addition, adjuvant radiation should not be considered a replacement for suboptimal surgical therapy: subtotal resection appears inferior to GTR, even when peri-operative RT is added to the former.

Interestingly, pre-operative embolization was not associated with any of the endpoints we explored. In our experience treating SFT/HPC, pre-operative angiography with embolization of tumor-feeding vasculature decreases blood supply to the tumor, decreasing operative time and blood loss; our previously noted observations coincide with those of others treating SFT/HPC. These potential benefits of peri-operative embolization have a much shorter latency than the tumor control endpoints that were the primary focus of this study. The limited number of patients available prevented an assessment of potential benefits of peri-operative embolization.

Era of treatment was associated with any CNS relapse and PFS. Interestingly, treatment in the more recent era was associated with inferior outcomes. Our data indicate that this is likely due to the differing age populations treated in the two eras, with younger patients predominating earlier. It is reasonable to suppose that younger patients generally have better outcomes, likely due to better performance status and less co-morbidities. From a technical standpoint, the introduction of intraoperative neurophysiological monitoring and, perhaps most importantly in this hemorrhagic tumor, pre-operative embolization may have allowed attempted surgical resection more recently in patients who would not have been candidates in earlier times.

Development of extraneural metastatic disease has a long latency after surgical resection, as the median time-to-extraneural metastasis was 248 months (95% CI 180-Not Reached). There was no clinico-pathologic predictor of extraneural metastasis reaching statistical significance. All eight patients developing extraneural metastases had tumors that were grade 3 at initial diagnosis. In the largest systematic review to date, including 71 studies with 2013 total patients, tumor grade was significantly associated with both local recurrence risk and development of extraneural metastases. Similarly, Ratneswaren et al reported that the risk of extraneural metastasis with grade 3 tumors was 1.88 times more likely, as compared to grade 1 and grade 2 tumors. Another series of 25 patients did not observe an association between SFT/HPC tumor grade and risk of extraneural metastasis. Peri-operative RT to the primary tumor site, a local treatment, was not associated with decreased risk of extraneural metastasis, consistent with our data.

Standard surveillance protocols for SFT/HPC after primary treatment are not established. After primary surgery, patients may experience recurrence years, or even decades, later. Prolonged surveillance is therefore justified, although the manner in which it is undertaken (for example, planned imaging versus imaging in response to clinical signs or symptoms) is not clear. We observed local recurrences in 18 (53%), extraneural metastases in 8 (24%), and neuraxial metastases in 3 (9%). These proportions are remarkably close to the 52%, 23%, and 6%, respectively, reported by Ghose et al in their systematic review. In addition, the locations of extraneural metastatic disease (lung 4/50%, liver 4/50%, bone 3/38%), seem to reflect the pattern of such metastases reported by others, although a higher relative proportion of bone metastases were reported by Ratneswaren et al.

Recommendations for follow-up are quite heterogeneous and include various imaging modalities, follow-up intervals, and total duration of follow-up. Damodaran et al reported monitoring for pulmonary metastases with plain radiographs.
every 6–12 months. CT body imaging every 6–12 months is utilized by others. Purandare reports using PET/CT for follow-up. At our center, routine follow-up for SFT/HPC patients after resection includes cranio-spinal MRI every 3 months following initial resection. In addition, CT imaging of the body is undertaken annually. Interval of follow-up for both CNS and body imaging gradually increases to annual cranial-spinal MRI and CT body imaging. This continues over the lifetime of the patient, due to data suggesting metastatic potential many years following initial diagnosis.

Admittedly, this regime involves the inconvenience and cost of obtaining these imaging studies, and radiation exposure associated with the CT imaging component. It is possible that symptom-driven assessment could be used to guide body imaging, given that interventions to address extraneural metastatic disease are likely to be less effective at achieving long-term control, particularly if disease is present at multiple distant sites. In contrast, we believe that a strong case can be made for ongoing CNS imaging with MRI. For the majority of patients, SFT/HPC recurs intracranially. Since local recurrence is the dominant treatment failure mode, with distant CNS disease being much less common, longitudinal surveillance imaging could be limited to the primary site, simplifying follow-up. This would focus follow-up evaluations on the most likely area of recurrence, in which early neurosurgical intervention may have the greatest benefit to prevent deterioration and debility from tumor progression.

The NAB2-STAT6 fusion protein that defines SFT/HPC may provide a more efficient and rational approach to monitor patients for evidence of disease recurrence. Detection of circulating tumor DNA (ctDNA) provides a means to detect this target, which could serve as a global indicator of the presence of active disease, prompting radiological evaluation. A number of commercial platforms are in development, or, in some cases in use, which might be exploited to monitor patients with SFT/HPC postoperatively. Such technology could allow more conservative use of radiological imaging.

One motivation for our study was to explore endpoints that might be useful in clinical trials. To this end, we derived estimated clinical outcomes (see Supplemental Materials, Table 1), which included 95% confidence intervals. These data suggest that short-term study endpoints of less than 3 years duration are impractical. The composite endpoint PFS might be useful for studies for which a duration of 3–5 years is assumed. Accrual to such a study, even with a compelling question, would be problematic. Our own center and other referral centers have required decades to accrue even the modest numbers of patients reported in single-institution, retrospective studies. Only a multi-institutional effort, such as through the cooperative group mechanism, could hope to accrue an adequate number of patients in a reasonable time period.

Instead, we identify several areas for research in SFT/HPC likely to have a greater immediate impact. First, studies to improve perioperative therapy could have short-term endpoints that are evaluable more rapidly. For example, prospectively documenting the benefits of pre-operative embolization could establish the technique as a standard component of SFT/HPC care. Second, developing surveillance technologies, such as through the evaluation of ctDNA, could provide more uniform and rational surveillance plans for SFT/HPC patients. Treatment failure by detection of ctDNA may emerge much sooner than radiological evidence of progression. Third, development of new systemic therapies for SFT/HPC must be a priority. Given the long survival of patients with this condition, the pool of patients living with recurrences would provide a large group of potential study subjects.

Our study has several limitations that are inherent to its design. Retrospective analyses can have a variety of biases. We have attempted to identify at least one such apparent bias in our results, in which patients treated in 1990–2008 had superior CNS recurrence and PFS, versus those from the 2009–2020 era. This was seemingly due to the differing age distributions in the two eras. However, the small sample size (n = 34) prevented us from constructing multivariable models that might have allowed better analysis of the relationships between variables. Thus, confounding cannot be easily controlled in our regression analyses. The small size also led to our confidence interval estimates for the various endpoints being very broad. Systematic reviews attempt to address size limitations by considering studies collectively, but are themselves limited by the variability in the designs of the underlying studies. For rare conditions such as CNS SFT/HPC, retrospective studies such as ours may be a dominant source of information, despite potential biases of such designs. In light of these limitations, we have attempted to be conservative in our conclusions. Analysis of information from larger data sets, such as the Surveillance, Epidemiology, and End Results database of the National Cancer Institute,
or the National Cancer Database of the American College of Surgeons, may allow further exploration and refinement of the results of our analysis.

**Conclusions**

SFT/HPC is a rare intracranial malignancy that appears to benefit from aggressive surgical resection and peri-operative RT. We found that age, extent of resection, and adjuvant radiation were prognostic variables associated with one or several outcome variables, including local disease recurrence, global CNS recurrence/metastasis, and PFS. Recurrent disease, including in extraneural locations, can occur years or even decades after initial therapy, warranting prolonged longitudinal surveillance.

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