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TOPIC REVIEW

Surveillance for metastatic hemangiopericytoma-solitary fibrous tumors-systematic literature review on incidence, predictors and diagnosis of extra-cranial disease

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Abstract

Background Intracranial hemangiopericytomas (HPC) and solitary fibrous tumors (SFTs) (HPC-SFT) are rare vascular tumors that resemble meningioma on imaging and predominantly affect young adults. HPC-SFT have a high rate of local recurrence with well-known propensity for extracranial metastases. This provides clinical dilemmas frequently encountered in oncology: (i) How should these patients be monitored long term? (ii) Which primary tumors are more likely to metastasize?

Objectives This systematic review aims to identify the incidence, common locations and time to presentation of extra-cranial metastases of HPC-SFT. We will assess the effect of primary tumor location, treatment, grade, patient age, gender and effect of local recurrence on rates of extra-cranial metastasis and discuss the ideal techniques by which patients with intracranial HPC-SFT should be monitored for extra-cranial metastases.

Methods Using PRISMA guidelines the authors searched Pubmed. Search terms included hemangiopericytoma, HPC, solitary fibrous tumor/ tumour, SFT, HPC-SFT, extra-cranial metastases, metastases, recurrence, monitoring, follow-up. Studies were identified up to 1st February 2018. Reference lists of identified articles were reviewed to detect other relevant citations. Data were extracted using a standard data collection form and results organized into (i) general study/patient characteristics, (ii) location of extra-cranial metastases, (iii) methods by which metastases were detected and followed up and (iv) characteristics of primary tumors.

Results Seventy-one studies were identified. Mean recorded follow up ranged from 4 to 312 months. Mean age at diagnosis was 42.0 years. The overall rate of extra-cranial metastasis was 28% (n = 251/904). The minimum time to extracranial metastases was 3 months and the maximum time was 372 months. In the 71 studies identified, where site of extra-cranial metastasis was specified, there were 347 metastases in 213 patients. The most common sites for metastases were bone (location not specified) (19.6%) followed by lung and pleura (18.4%), liver (17.6%), and vertebrae (14.1%). Extra-cranial metastatic disease is typically diagnosed following symptomatic presentation. There is little documentation of methods used to monitor patients with extra-cranial HPC-SFT and no clear surveillance paradigm observed. Higher primary tumor grade (WHO Grade III) was associated with a 1.88 (p = 0.016) increased risk of extra-cranial metastasis. Location and treatment of primary tumor, local recurrence, patient age and gender were not.

Conclusion Patients with intracranial HPC-SFT require periodic, long term monitoring for extra-cranial metastases. Metastases occur in any age group and can occur early and late. They vary in location and are typically diagnosed following symptomatic presentation. There is no suggested imaging modality for surveillance. Higher grade primary tumors have a greater risk of metastasis. Regular clinical review is essential with early imaging for symptoms of recurrence/metastasis with imaging modality dependent on clinical concern. Quality evidence for an imaging surveillance protocol in this heterogeneous group of patients is lacking. A multicenter study on appropriate surveillance may be of benefit.

Keywords Hemangiopericytoma · Solitary fibrous tumor · Extra-cranial metastases · Monitoring · HPC · SFT

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Introduction

Hemangiopericytoma (HPC) and Solitary Fibrous Tumors (SFTs) are rare vascular malignancies that derive from Zimmerman's pericytes, modified smooth muscle cells that line capillaries, postcapillary venules and sinusoidal spaces [1]. Primary HPC-SFT tumors occur at various sites across the body; the most common sites for HPC-SFT are the thigh (25.5%), pelvic retroperitoneum (24.5%) and head and neck (16.0%) [2]. HPC-SFT predominantly affect young adults with an average age at diagnosis of 41–48 years [3–5].

Intracranial HPC-SFT tumors are rare (0.4% of all primary CNS tumors), slow growing, extra-axial tumors that radiologically and macroscopically resemble meningioma. HPC-SFT account for around 2.4% of suspected meningiomas [3] and often the diagnosis is made during resection where HPC bleed profusely. Despite their similar appearance and location to meningioma on imaging, intracranial HPC are more aggressive, more likely to recur locally and to metastasise [3].

The World Health Organization (WHO) classification of Central Nervous System tumors (1993) defines HPC as a distinct class from meningioma [6] and in the 2016 update from previous classifications, HPC have been reclassified combining previously named solitary fibrous tumors with traditional HPC. The tumors have been grouped together as there is a growing body of evidence that both HPC and SFT share similar histological [7] and immunohistochemical appearances [7, 8] and cannot be reliably differentiated. Conventionally low (WHO I) grade tumors with low cellularity and a 'patternless architecture' were classified as SFT, WHO II tumors are described as HPC and higher grade (WHO III) tumors with increased cellularity and mitotic number were classified as anaplastic HPC.

Intra-cranial HPC-SFTs are usually managed with surgical resection. Extent of resection is correlated with survival [4, 5] but does not reduce the probability of local recurrence or extra-cranial metastases [4, 5]. Although it has not been investigated robustly, there is evidence to suggest that grade of tumor is related to likelihood of tumor recurrence [9, 10] but has no confirmed association to extra-cranial metastasis [3, 11, 12]. Post-operative periodic follow-up cranial imaging is routine but screening for extra-cranial disease and the most appropriate imaging modality for this remains a question faced by neuro-oncology multi-disciplinary teams.

In this systematic review we discuss the frequency and location of *extra-cranial* metastases in patients with confirmed intra-cranial HPC or SFT. We investigate the factors that may predispose patients to extra-cranial metastasis and consider evidence for routine monitoring for extra-cranial disease and the appropriate imaging modality for this purpose.

Materials and methods

Criteria for considering studies for this review

All studies published from 1/1/1980 to 01/02/2018 that describe primary intracranial HPC and/or SFT with extracranial metastases were included in this study. Studies published before 1980 or in languages other than English were excluded as were papers in which it was unclear whether the primary tumor was intra or extracranial. Orbital primary tumors were also excluded from the analysis.

Literature search methods

Based on the PRISMA guidelines, the authors searched Pubmed (http://www.ncbi.nlm.nih.gov/pubmed). Studies were identified up to 1st February 2018. Search terms included intracranial, hemangiopericytoma, HPC, solitary fibrous tumor/tumor, SFT, metastases, extra-cranial metastases, recurrence, recurrent, imaging, MRI, CT, PET, monitor and follow up. Reference lists of identified articles were reviewed to detect other relevant citations.

Data extraction and management

Data were extracted using a standard data collection form created for this review. Extracted data consisted of study characteristics (number of participants, mean age, gender, follow-up length), details of the primary disease (age of onset, location, tumor grade, treatment, local recurrence) and details of extra-cranial metastases (location, time to diagnosis, methods of detection ± imaging modality for diagnosis, suggested systemic monitoring protocols where applicable).

Statistical analysis

Univariate logistic regression was performed in SPSS for the following variables: age, gender, primary tumor grade, local recurrence, surgical treatment (gross total resection vs. subtotal resection), adjuvant treatment to initial primary disease (external beam radiotherapy, stereotactic radiotherapy, proton beam therapy, chemotherapy) on the likelihood that patients would develop extra-cranial metastasis. The logistic regression model was considered statistically significant, $\chi^2(4) = 27.402$, $p < 0.0005$.

Multivariate logistical regression was not performed as a complete data set was only present in 27 patients.

Results

Seventy-one studies [3–5, 9–76] were identified documenting 904 cases of HPC-SFT and 251 cases of extra-cranial metastasis. Study characteristics and details of the primary tumor and management, where given, are shown in Table 1 [3–5, 9–76]. Follow up duration was not always documented but the mean recorded follow up ranged from 4 [66, 72] to 312 months [74]. Mean age at diagnosis of primary tumor for patients in all studies was 42.0 years.

Duration of follow up

The rate of extra-cranial metastases following a diagnosis of primary intra-cranial HPC or SFT ranged from 3.7 [46] to 69.0% [77] in all case series to 6.3 [13] to 69.0% [77] in case series with follow up of over 60 months (5 years). In those case series with a long follow up of almost a decade (> 9 years) there was a 11.6 [5] to 69.0% [77] rate of extra-cranial metastases. Range of time to extracranial metastases was from 3 [76] to 372 months [16] (Table 1).

Location of extra-cranial metastasis

Intra-cranial HPC-SFT can metastasize to multiple extra-cranial sites (Table 2). The most common sites for metastases were Bone NOS (location not otherwise specified) (19.6%) followed by lung and pleura (18.4%), liver (17.6%), and vertebrae (14.1%). Further sites of metastases listed include kidney, pelvic bones, femur, pancreas, retroperitoneum, peritoneum, the soft tissues, skin, muscle, ocular, breast, adrenal gland and metastases not otherwise specified.

Predictors of extracranial metastasis

Tumor grade

Details of tumor grade were documented in 301 cases. High grade primary tumors (WHO Grade III n = 108) were 1.88 times as likely to metastasize extra-cranially as low grade tumors (WHO Grade I and WHO Grade II n = 193) (p = 0.016). WHO Grade III HPC (n = 108) were 2.53 times as likely to metastasize as WHO Grade II (n = 175) (p = 0.001).

When comparing the rates of extra cranial metastasis from WHO Grade II (n = 175) to WHO Grade I (n = 18) the Odds Ratio (OR) was 0.89 (p = 0.000017), indicating a higher rate in Grade I patients, which is a surprising result. As the majority of papers (11/13) [15, 17, 21, 22, 27, 54, 70–75] that discussed WHO grade I tumors were case reports, this analysis likely over emphasises the frequency of metastatic disease in this tumor grade. Furthermore in six cases of extra-cranial metastasis in WHO Grade 1 tumors [15, 17, 21, 27, 54], the primary tumor was originally classified as a low grade meningioma and later revised to HPC, which might raise the possibility of misdiagnosis.

Age

Age was given in 184 cases. When divided into 'younger' [0–40 (n = 101)] and 'older' [41–90 (n = 83)] older age at first diagnosis were less likely (OR 0.585) to develop extra-cranial metastasis but this was not statistically significant (p = 0.74).

Sex

Gender was recorded in 184 cases. Men (n = 93) were 1.197 times as likely to develop an extra-cranial metastasis as women (n = 91) but this was not statistically significant (p = 0.544).

Tumor location

Tumor location was accounted for in 155 cases. A posterior fossa location for the tumor had a higher chance of metastasizing when compared to a supratentorial lesion (OR 2.250) but this was not statistically significant (p = 0.76).

Local recurrence

Data was recorded for all patients with extra-cranial metastasis who had local recurrence prior to a diagnosis of metastasis and all patients without extra-cranial metastasis who had local recurrence (n = 352). Local recurrence was not predictive for developing extra-cranial metastasis (OR 0.794, p = 0.343).

Surgery

All patients underwent surgical intervention although the extent of surgery was not always specified. In those patients of whom extent of surgery was reported (n = 333) there was no difference in rates of extra-cranial metastasis between those with gross total resection (GTR) (n = 259) and those with subtotal resection (STR) (n = 74) (OR 0.644, p = 0.151).

Adjuvant therapy

Patients whose primary tumor was treated with adjuvant radiotherapy [either external beam radiotherapy (EBRT) or Stereotactic radiosurgery (SRS) n = 209/413] were more likely to develop extra cranial metastasis but this was not statistically significant (OR 1.24, p = 0.335). This may reflect

Table 1 Details of the included studies: number of patients with extra-cranial metastases, average time to metastasis and details on the grade and treatment of the primary tumors for those patients

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
1	Guthrie [3]	1989	44	42	> 180*	10 (22.7)	24	240	99	8 (80)	NS					10 (100)					Grade of tumor did not correlate with rate of recurrence, metastasis or survival
2	Rutkowski [4]	2012	35	48	NS	7 (20)	NS	NS	NS	NS	NS			1 (14)	1 (14)	4 (57)	2 (14)				Extent of resection nor post operative radiotherapy prevented nor extended the time to the development of metastasis. Adjuvant radiation decreased the rates of progression and recurrence but had no effect on survival

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
3	Melone [5]	2014	43	46.9*	118*	5 (11.6)	NS	NS	NS	NS			5 (100)	1 (20)	1 (20)	1 (20)	2 (40)					No evidence that extent of resection or adjuvant RT could prevent or extend the development of metastatic HPC
4	Damodaran [39]	2014	25	42*	204.6*	8 (32)	NS	NS	NS	0		5 (62)	3 (38)	NS								No evidence that extent of resection or adjuvant RT could prevent or extend time to peripheral metastasis
5	Ramakrishna [13]	2014	16	51.0	91	1 (6.3)	NS	NS	NS	NS	NS			NS								No comment on location of one case of extracranial metastasis. Study does indicate that total resection reduces recurrence rates
6	Zhou [14]	2012	39	41.7	NS	2 (5.1)	NS	NS	NS	NS			2 (100)	NS								
7	Anderson [15]	1980	1	25	84	1	10	10	10	1 (100)	1 (100)**			1 (100)								

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
8	Kumar [10]	2012	15	40*	44*	1 (6.7)	60	60	60	NS	NS			NS							No details given on specifics of patient with metastasis but the study concluded that Grade III tumors have higher rates of recurrence and poorer outcomes
9	Sheehan [11]	2002	14	49	31	2 (14.3)	NS	NS	NS	2 (100)	NS					2 (100)					Paper is assessing use of SRS in recurrent intracranial HPC. Of those with recurrence Rx with SRS 2/14 had extracranial metastasis

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor								
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
10	Galanis [12]	1998	34	48*	NS	17 (50)	NS	NS	NS	17 (100)		9 (53)	8 (47)	NS								No details on treatment regimens prior to disease recurrence. Article describes treatment modalities for recurrent disease
11	Schiariti [16]	2011	39	44	123	9 (23.1)	56	372	123	NS	NS			NS								No data included on treatment of the primary tumors but paper reported the metastasis free period was longer in those with complete surgical resection (170 vs. 100 months respectively, p = 0.5) and EBRT (139 vs. 68 months respectively, p = 0.2)

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]												Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor								
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
12	Suzuki [17]	2002	1	42	276	1	276	276	276	1 (100)	1 (100)**			1 (100)								
13	Hiraide [18]	2014	1	41	288	1	204	288	246	0	NS			1 (100)								
14	Fountas [19]	2006	11	51	85.2	4 (36.4)	30	84	58.5	2 (50)	NS						4 (100)					
15	Ambrosini-Spaltro [20]	2010	14	53	96	1 (7.1)	156	156	156	1 (100)		1 (100)		1 (100)								
16	Tanabe [21]	1984	1	50	180	1	180	180	180	0	1 (100)**			1 (100)								
17	Teh [22]	2000	1	41	84	1	84	84	84	1 (100)	1 (100)**			1 (100)								
18	Iwamuro [23]	2008	1	44	192	1	108	120	114	0	NS			1 (100)								
19	Sun [24]	2009	22	41	67.7	3 (13.6)	12	180	78	3 (100)	NS					2 (66)					1 (33)	
20	Nickerson [25]	2015	1	40	276	1	228	288	264	1 (100)		1 (100)		1 (100)								
21	Eil [26]	2012	1	34	120	1	120	120	120	1 (100)			1 (100)	1 (100)								
22	Chang [27]	2004	1	43	60	1	60	72	66	1 (100)	1 (100)**			NS								
23	Wei [28]	2015	1	36	60	1	48	48	48	1 (100)		1 (100)		1 (100)								
24	Chan [29]	2010	1	42	7	1	84	84	84	0	NS					1 (100)						
25	Nair [30]	2010	1	16	60	1	60	60	60	0			1 (100)	1 (100)					1 (100)			
26	Jaaskelainen [31]	1985	18	39	91	3 (16.7)	52	77	62	1 (33)	NS			2 (66)	1 (33)							

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
27	Olson [32]	2010	21	47*	68*	4 (19.0)	NS	NS	NS	1 (100)	NS			NS							All patients included had recurrent disease. At primary diagnosis all had been treated with surgery and adjuvant therapy which is not detailed. Univariate logistic regression reported in paper states progression of intracranial lesions does not correlate with the development of extracranial metastasis ($p > 0.05$)

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor								
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
28	Chang [33]	2003	8	45.1	44	1 (12.5)	12	12	12	1 (100)	NS			NS							
29	Mena [9]	1989	94	40.9	NS	17 (18.1)	NS	NS	NS	14 (77)		6 (36)	11 (64)	NS							Large study. Anaplastic recurrence was considered a risk for recurrent tumor OR 3.3 ($p=0.043$) but not metastatis 2.81 ($p=0.41$). Infiltration of brain parenchyma OR 7.0 and male gender OR 4.89 ($p<0.05$) were both factors assoc with higher rates of metastasis
30	Kano [34]	2008	20	51.5*	48.2	5 (25)	NS	NS	NS	5 (100)	NS			NS							

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
31	Ecker [35]	2003	38	40	97.2	11 (28.9)	NS	NS	NS	NS	NS			NS							Analysis showed metastatic disease had poor prognosis with high mortality. No data on risk factors for metastasis but neither extent of resection, post operative EBRT, low tumor grade, tumor location, patient age nor sex were associated with a survival benefit
32	Kim [36]	2003	31	41	77	4 (12.9)	31	192	107	2 (50)	NS			2 (50)		1 (25)	1 (25)				
33	Hara [37]	1998	2	35	24	1 (50)	13	13	13	1 (100)		1 (100)			1 (100)						

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
34	Chen [38]	2015	38	38.5	61	5 (13.2)	20	90	54	NS	NS					2 (50)				2 (50)	GTR was not shown to significantly reduce chance of metastatic disease. Low grade tumors had a longer time to recurrence and metastasis
35	Soyuer [40]	2004	29	42*	112	20 (69.0)	7	217	97*	NS	NS			NS							NO evidence that resection or post op RT had an affect on development of extracranial metastasis
36	Dufour [41]	2001	17	40.8	60	3 (17.6)	144	180	160	2 (66)	NS			2 (66)		1 (33)					
37	Fukuda [42]	2015	1	19	204	1	204	204	204	0		1 (100)							1 (100)		
38	Noh [43]	2015	15	47.2	53	2 (13.3)	41	78	59.5	0	NS			1 (50)					1 (50)		
39	Begum [44]	2002	1	41	204	1	204	204	204	1 (100)		1 (100)		NS							
40	Chan [45]	2012	1	37	84	1	84	84	84	1 (100)		1 (100)				1 (100)					
41	Cao [46]	2006	1	25	120	1	120	120	120	1 (100)	NS			1 (100)							

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]												Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
42	Spatola [47]	2004	1	48	144	1	102	114	102	1 (100)		1 (100)		1 (100)								
43	Chacko [48]	2006	27	31.3	49	1 (3.7)	17	17	17	0	NS			NS								Conclusions that a high proportion of intracranial HPC recur despite radical excision and adjuvant EBRT
44	Heiser [49]	2009	5	46	87.4	1 (20)	60	60	60	1 (100)	NS					1 (100)						
45	Yesikaya [50]	2012	1	60	132	1	108	108	108	1 (100)	NS					1 (100)						
46	Pistolesi [51]	2004	1	42	156	1	156	156	156	1 (100)	NS			1 (100)								
47	Grunenberger [52]	1999	1	31	163	1	132	132	132	1 (100)	NS			1 (100)								
48	Nonaka [53]	1998	1	39	116	1	96	116	104	1 (100)	NS			1 (100)								
49	Siegal [54]	2012	1	38	240	1	156	156	156	1 (100)	1 (100)**			1 (100)								
50	Satayasoontorn [55]	2014	4	46	NS	4	84	120	99	1 (25)	NS			3 (75)		1 (25)						
51	Woitzik [56]	2003	1	40	96	1	96	108	102	0			1 (100)			1 (100)						
52	Lee [57]	2004	1	47	78	1	78	78	78	0	NS					1 (100)						
54	Kim [59]	2016	18	38*	119.6	7 (38.9)	NS	NS	96.3*	7 (100)			7 (100)	3 (43)		4 (57)						
55	Lo [60]	2016	5	24.2	34.2	5	60	228	141.6	NS	NS			NS								
56	Purandare [61]	2010	1	21	96	1	96	96	96	0	NS					1 (100)						
57	Manatakis [62]	2015	1	23	156	1	84	84	84	1 (100)		1 (100)		1 (100)								

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor							
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
58	De Martin [63]	2015	1	44	53	1	48	72	60	0	NS			1 (100)								
59	Doxtader [64]	2015	1	29	216	1	168	168	168	1 (100)			1 (100)				1 (100)					
60	Nakada [65]	2015	2	52.5	132	2	108	156	132	1 (50)	NS			1 (50)		1 (50)						
61	Ramos [66]	2014	1	52	4	1	4	4	4	0	NS					1 (100)						
62	Fabbri [67]	2014	1	62	84	1	84	84	84	1 (100)	NS			1 (100)								
63	Delgado [68]	2011	1	65	84	1	72	72	72	1 (100)	NS										1 (100)	
64	Han [69]	2016	19	44.5	160	10 (52.6)	67	290	170	7 (70)	NS			5 (50)		4 (40)				1 (10)		
65	Degnan [70]	2017	1	29	126	1	120	120	120	0	1 (100)									1 (100)		
66	Kim [71]	2004	4	32.7	34.5	1	84	84	84	NS	1 (100)			1 (100)								
67	Wu [72]	2015	1	25	4	1	4	4	4	1 (100)	1 (100)			1 (100)								
68	Ng [73]	2000	1	47	119	1	108	108	108	1 (100)	1 (100)					1 (100)						
69	Ogawa [74]	2004	1	44	312	1	300	300	300	1 (100)	1 (100)			1 (100)								
70	Gessi [75]	2013	1	53	204	1	108	108	108	1 (100)	1 (100)			1 (100)								

Table 1 (continued)

		Year	N	Age (M/y)	Follow up (M/m)	Patients with extracranial metastasis (N/%)	Minimum time to metastasis (m)	Maximum time to metastasis (m)	Time till metastasis (M/m)	Patients with extracranial metastasis [n (%)]											Comments
										Local recurrence preceding metastasis (N/%)	Grade of primary tumor (N/%)			Treatment to primary tumor								
											WHO G I	WHO G II	WHO G III	GTR	STR	GTR + EBRT	STR + EBRT	GTR + EBRT + SRS	GTR + SRS	STR + SRS	B + SRS	
71	Cohen-Inbar [76]	2017	90	48.5*	59*	22 (24.4)	3	108	21.5	22 (100)	NS			NS							Large multicentre study looking at outcomes for patients with HPC (79% grade 2), all of whom at some point had surgery and SRS with or without other adjuvant Rx. It is not clear if SRS was part of initial treatment

M mean unless, *y* years, *N* number, *m* months, *NS* not specified, *GTR* gross total resection, *STR* sub-total resection, *EBRT* external beam radiotherapy, *SRS* stereotactic radiosurgery, *B* biopsy

*Median

**Initial histology reported as Grade 1 meningioma

Table 2 Location and number (no.) of extra-cranial metastases (metastasis) from primary intracranial HPC-SFT where site of metastasis was specified

Location of mets	No. of mets (%)
Bone NOS/other	68 (19.6)
Lung and/or pleura	64 (18.4)
Liver	61 (17.6)
Vertebrae	49 (14.1)
Kidney	14 (4.0)
Pelvic bones	11 (3.2)
Femur	11 (3.2)
Pancreas	10 (2.9)
Retroperitoneum	4 (1.2)
Peritoneum	3 (1.0)
Other	52 (15.0)

Percentages (%) are given as a proportion of metastasis occurring at each site. Each individual metastasis counts as one 'Metastasis'. Some patients had multiple metastases

the fact that radiotherapy is more likely to be used in the higher grade tumors.

When the types of adjuvant treatment to the primary tumor were subdivided [EBRT (n = 180), SRS (n = 24), Proton beam therapy (PBT) (n = 1), EBRT + chemotherapy (n = 3), EBRT + SRS (n = 1)] there was no statistically different outcomes compared with those who had no adjuvant treatment.

Diagnostic techniques for extra-cranial metastasis

Of the 71 papers identified, documentation of methods used to monitor patients with intra-cranial HPC for extracranial metastases was poor (Table 3). One group followed up patients with metastases with annual clinical review and Computed Tomography (CT) of abdomen, pelvis and chest [25]. One study documents discovery of a non-symptomatic pancreatic metastasis on a routine follow up CT scan 24 years after the initial tumor diagnosis. In one study where a patient developed pulmonary metastases, the authors recommend that all patients with intra-cranial HPC are monitored with chest X-rays at 6–12 month intervals to screen for metastases [39]. Overall the interval length of scans, length of follow up, imaging modality of choice and regions imaged were not well defined [18].

Discussion

In this review we have demonstrated that extra-cranial metastases of intra-cranial HPC-SFT are common, occurring in 28% of cases reviewed (n = 251/904). Removing case reports from this statistic, which are inherently biased to discuss the rarer cases with metastatic disease, the prevalence of extra-cranial metastasis becomes 23% (n = 202/868). When this is adjusted for studies with follow up of greater than one decade, it is shown that 1 in 1.4–8.6 people with primary intra-cranial HPC-SFT will develop extra-cranial metastases. The broad width of this estimate reflects the lack of prospective observational studies looking into the natural progression of these patients; all studies assessed were case series with variable durations of follow up. Furthermore our review demonstrates that metastases from HPC/SFT can develop at variable times after the primary tumor diagnosis, both around the time of the primary HPC or as long as 31 years after the initial diagnosis which may mean the above value underestimates extra-cranial metastases. HPC can affect patients at all stages of life but is most commonly observed in the young. Given the length of time at which metastasis can occur, life-long close clinical monitoring for intra-cranial recurrence and extra-cranial metastases is therefore recommended and supported by the literature.

Our review has demonstrated that the common sites for metastases of primary intra-cranial HPC are bone, lung, liver, other abdominal structures as well as multiple other sites across the body. This is in contrast to locations of primary HPC-SFT tumors which commonly occur at the thigh, pelvic retroperitoneum and head and neck [2]. Due to the multiple sites of metastases from intra-cranial HPC-SFT, monitoring for metastases would require whole body imaging.

Radiological surveillance of patients with HPC for extra-cranial metastases would enable early recognition of disease occurrence and enable early intervention. For a diagnostic surveillance test to be useful, it should be inexpensive, easy to administer, cause minimal discomfort or harm, and demonstrate a high sensitivity and specificity. An imaging surveillance protocol should consider (1) the time period for maximal risk of recurrence and interval between examinations (2) the most likely sites for metastases (3) treatment options if lesions were identified (4) the risks associated with the imaging modality [78]. So far there are no biological markers for HPC and imaging modalities (predominantly CT, Positron Emission Tomography (PET)-CT and MRI) are the main methods used to detect HPC. Some studies have recommended the use of whole body CT/PET in the regular monitoring of HPC patients [61]. PET provides metabolic information and the tracer is actively taken up by these highly vascular tumors. However whole body PET/CT scanning exposes patients to a substantial radiation dose and thus increased lifetime cancer risk [79]. For this reason we would argue PET-CT is not a suitable method for periodic, long-term monitoring of a relatively young patient population (although it has a potential role in diagnosis). Annual whole body CT scans in a 45 year old up till the age of 75

Table 3 Methods of detecting extra-cranial metastasis

1st author	Year	Method mets detected	Imaging modality detected	Monitoring of extracranial mets
Damodaran [39]	2014	NS	NS	Recommend-chest Xray at 6–12 month intervals to screen for pulmonary mets
Anderson [15]	1980	Symptomatic	X-ray	NS
Schiariti [16]	2011	NS	MRI	Clinical assessment and MRI for 5–15 years
Suzuki [17]	2002	Symptomatic	MRI	NS
Hiraide [18]	2014	Renal and lung-symptomatic, pancreas-follow up CT	CT	Routine interval CT after initial symptomatic mets, interval length not specified
Tanabe [21]	1984	Symptomatic	CT	No regular review
The [22]	2000	Symptomatic	CT	No regular review
Iwamuro [23]	2008	Symptomatic	US, CT and MRI	NS
Nickerson [25]	2015	Symptomatic	CT	Annual clinical review with CT-chest, abdomen, pelvis in patient with mets
Eil [26]	2012	Symptomatic	MRI and CT	Nil
Chang [27]	2004	Symptomatic	CT	NS
Wei [28]	2015	NS	MRI and CT	NS
Chan [29]	2010	Symptomatic	18F-FDG-PET-CT	Annual review-method not specified
Nair [30]	2010	Symptomatic	18F-FDG-PET-CT	No regular review
Hara [37]	1998	Symptomatic	NS	NS
Fukuda [42]	2015	Symptomatic	MRI	NS
Begum [44]	2002	Symptomatic	MRI	NS
Chan [45]	2012	Symptomatic	CT	NS
Cao [46]	2006	Symptomatic	CT	Nil
Spatola [47]	2004		CT	NS
Heiser [49]	2009	PET/CT after intracranial recurrence	CT/PET	Nil
Yesikaya [50]	2012	Symptomatic	US and CT	NS
Pistolesi [51]	2004	CT after intracranial mets	CT	NS
Grunenberger [52]	1999	Symptomatic	CT	NS
Nonaka [53]	1998	Symptomatic	CT and MRI	Patient declined bone scintigraphy
Siegal [54]	2012	Symptomatic	X-ray and MRI	NS
Satayasoontorn [55]	2014	Symptomatic	CT	Nil
Woitzik [56]	2003	Symptomatic	MRI	NS
Lee [57]	2004	Symptomatic	MRI	Nil
Taniura [58]	2007	Symptomatic	MRI	Nil
Lo [60]	2016	NS	CT in 3/5	NS
Purandare [61]	2010	Symptomatic soft tissue mass then PET/CT	PET/CT	Nil
Manatakis [62]	2015	Incidental finding on CT	CT	NS
De Martin [63]	2015	Symptomatic then CT	CT	NS
Doxtader [64]	2015	Staging CT	CT	NS
Nakada [65]	2015	Symptomatic then CT	CT	NS
Ramos [66]	2014	Symptomatic then MRI	MRI	NS
Fabbri [67]	2014	Symptomatic then CT	CT	NS
Delgado [68]	2011	Symptomatic then CT	CT	NS
Han [69]	2016	NS	NS	NS
Degnan [70]	2017	Symptomatic then CT	CT	CT at 6M
Kim [71]	2004	Symptomatic then X-ray then CT	X-ray then CT	Annual clinical review
Wu [72]	2015	Symptomatic then PET/CT	PET/CT	NS
Ng [73]	2000	Symptomatic then CT	CT	NS

Table 3 (continued)

1st author	Year	Method mets detected	Imaging modality detected	Monitoring of extracranial mets
Ogawa [74]	2004	NS	X-ray, CT, MRI	NS
Gessi [75]	2013	Intracranial recurrence with pre-operative CXR	X-ray, CT	NS
Cohen-Inbar [76]	2017	Staging imaging	CT, MRI	NS

NS not specified, *GD* gadolinium, *MRI* magnetic resonance imaging, *CT* computed tomography

(30 scans) would contribute an additional lifetime risk of cancer mortality of 1.9% [80].

Serial whole body MRI scans are more expensive and more time consuming than CT [81]. However MRI does not expose the patient to harmful radiation and it is more sensitive in picking up soft tissue abnormalities; including early bone marrow infiltration in bony metastatic disease. Previous studies have demonstrated the use of whole body MRI in the monitoring of metastases in patients with saracomas [81]. The sensitivity and specificity of whole body MRI for detecting HPC metastases requires further investigation, as there is no literature on this.

Our review has shown no paradigm for imaging surveillance for HPC/SFT metastatic disease. Most extra-cranial disease was recognized on symptomatic presentation. Although survival data in the studies reviewed was lacking, we found no evidence to suggest that early detection of metastases affects outcome in this population and so cannot conclude that routine screening imaging is warranted in surveillance of extra-cranial metastases.

The only risk factor observed for extra-cranial metastasis, identified through the univariate logistic regression of the pooled studies, was the higher tumor grade (WHO Grade III have 1.88 increased risk when compared to WHO Grade I + II $p = 0.016$). None of the studies reviewed had independently observed this relationship. Mena et al. [9] found anaplastic tumors had a 3.3 higher risk of recurrence than lower grade ($p = 0.043$) and that extracranial metastasis were more frequent in anaplastic tumors but without statistical significance (OR 2.81 $p = 0.41$). Mena et al. [9] also found male gender and infiltration of the brain parenchyma to be associated with higher rates of metastasis (OR 7.0 and 4.8 respectively, $p = < 0.05$), which was not supported by our review. Whilst our analysis indicates that higher grade tumors have higher rates of metastasis, we have also shown extra-cranial metastasis occurring in patients of all tumor grades including SFT, which were previously described as benign and less likely to metastasize [69–75]. Clinicians therefore should be more cautious with tumors of higher grade but close clinical monitoring should not be restricted only to this group. This is an insight not previously emphasized in the literature on this tumor.

No previous studies found extent of surgical resection of the primary tumor nor the use of adjuvant radiotherapy to be related to rates of extra-cranial metastasis [3–5, 38, 39, 77], which is supported by our analysis. Schiariti et al. [16] reported a longer duration to extra-cranial metastasis in patients who had undergone gross total resection (170 vs. 100 months respectively, $p = 0.5$) and adjuvant external beam radiotherapy (139 vs. 68 months respectively, $p = 0.2$) but these findings were without statistical significance. Chen et al. [38] found radical resection with post-operative radiotherapy to improve overall survival and recurrence free interval ($p = < 0.05$) but had no effect on the metastasis free interval ($p = 0.245$).

Local recurrence was not an independent risk factor for extra-cranial metastasis, which is also supported by the independent findings of the studies assessed.

Conclusion

In this paper we have demonstrated that intracranial HPC can metastasize to extra-cranial sites over a long time course and variety of locations. A number of imaging modalities have been used in diagnosing extra-cranial disease including: X-ray, CT, CT-PET and MRI after patients present with symptoms. Few groups practice routine imaging surveillance to detect extra-cranial disease. There is no evidence based protocol and a wide variation in clinical practice. Higher grade of primary tumor (WHO Grade III) has a 1.88 increase risk of extra-cranial metastasis when compared to low grades (WHO I + II) but extra-cranial metastases have been seen in all tumor grades. Extent of surgical resection, location of primary tumor, use of adjuvant radiotherapy to the primary tumor, gender and patient age at first diagnosis were not influential on extra-cranial metastasis.

Our review is limited by the reliance on retrospective observational papers including 49 case reports, with varying degrees of patient follow up and clinical information. We were unable to perform a multi-variate logistic regression due to incomplete detail in many of the studies assessed (only 27 cases included information on all the variables assessed). Our univariate logistic regressions were also limited by numbers due to poor study detail.

Despite its limitations this review supports the importance of long term follow up and consistently high clinical suspicion for the possibility of extracranial metastases in HPC-SFT; including in the lower grade tumors. The use of diagnostic screening as a routine part of clinical follow up would require a multi-institutional discussion/study on the best options and given the heterogeneous group of patients and disease presentation may prove difficult to implement.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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