

The radiation therapy options of intracranial hemangiopericytoma: An overview and update on a rare vascular mesenchymal tumor

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Abstract

Hemangiopericytoma (HPC) is an extremely rare hypervascular tumor of mesenchymal lineage. It tends to recur and to develop distant metastases even many years after primary surgical resection. The management of recurrent and metastatic disease is not always so well defined. A complete surgical resection does not eliminate the high risk of local recurrences that occur in the central nervous system, often in the same surgical bed. However, treatment with adjuvant radiotherapy even in cases of complete resection remains controversial. Because of its rarity, there is no standard for treatment. We focused on radiotherapy treatment options, analyzing the literature and making a base on conduct further studies to establish the standard radiation dose to be used for locoregional control of such a complex and extremely rare disease and to help specialists to take the most appropriate therapeutic option.

Introduction

Hemangiopericytoma (HPC) is an extremely rare hypervascular tumor of mesenchymal lineage that arises from Zimmerman pericytes, the contractile cells surrounding vasculature around capillaries and post-capillary venules. HPC was first described by Stout and Murray in 1942¹ and it may occur anywhere in the human body because of the ubiquity of blood vessels, involving primarily the soft tissues of the limbs or the retroperitoneal and retropleural spaces, but also the larynx, the bones, the spleen or the central nervous system (BIBLIO). Intracranial HPCs mostly arise from the meninges of the brain and spinal cord². They con-

stitute less than 1% of all CNS tumors and <2.5% of all meningeal tumor¹. The first reported case of hemangiopericytoma originating in the meninges was described by Begg and Garret in 1954.³ Meningeal HPC were originally considered a variation of meningioma, and they were called “angioblastic meningiomas”. The inclusion of CNS HPCs as a distinct entity in the CNS tumors classification has been a matter of debate for many years until the World Health Organization distinguished them from meningiomas in 1993 classifying HPCs into the group of “mesenchymal, non-meningothelial tumors”⁴ thanks to its special clinical behavior, together with its immunohistochemical, structural and genetic characteristics.^{5,6,7,8,9} In the general pathology community, HPC is considered part of a spectrum with solitary fibrous tumor (SFT), with HPC representing a more biologically aggressive form. This classification approach has not yet been embraced by neuropathologists and is still under debate. The most recent World Health Organization (WHO) classification of the tumors of soft tissue considered the term HPC obsolete, and places all such tumors within the extrapleural SFT category. In contrast, CNS SFT and HPC continue to be regarded as different entities in the latest version of the WHO CNS tumor classification. A change in this approach is currently being considered for the upcoming revision of the WHO scheme. Now, these lesions are classified as World Health Organization (WHO) grade II (HPC) or WHO grade III (anaplastic HPC) lesions. Anaplastic HPC has a higher recurrence rate and the tendency to metastasize outside the CNS, typically to the liver, lungs, and bones, necessitating long-term close clinical and radiologic follow-up.

Because of its rarity, there is no standard for treatment. We focused on radiotherapy treatment options, analyzing the literature and making a base on conduct further studies to establish the standard radiation dose to be used for locoregional control of such a complex and extremely rare disease and to help specialists to take the most appropriate therapeutic option.

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Epidemiology

Most HPCs occur in adults, with a median age of 45-50 years. HPCs reportedly have a slightly higher preponderance among male individuals, and patients most often present with headaches. The majority of reported HPCs were supratentorial, but the tumors were found anywhere along the neuraxis.

Etiopathogenesis

The etiology of HPC is still a dilemma. When a hemangiopericytoma develops in a child, it is sometimes considered congenital. In some families, several members of a generation all have tumors. There could be a link between Hemangiopericytoma

development and a tendency to develop other tumors.

Multiple research groups successfully detected the specific gene fusion NAB2-STAT6 in both soft tissue SFT and HPC specimens. The fusion gene products promote tumor cell proliferation by activating the early growth response (EGR) gene and play an important role in HPC tumorigenesis.

Clinical aspects

The symptoms of this type of tumor are non-specific and often similar to those of other types of tumors, such as meningeal meningioma and they depend on the tumor size, extent, involvement of surrounding structures and position. Intracranial HPCs symptoms could be headache, dizziness, vomiting, weakness and blurred vision. Additional presenting symptoms included papilledema, hemiparesis, gait disturbance, and ataxia, depending on the localization of the tumor. Due to the intense vascularity, to the erosion, distortion or distension of great vessels and endothelial proliferation, MHCPs can also present as acute intracranial hemorrhage¹⁰ carrying the risk of life threatening massive bleeding.¹¹

Diagnostic tools

Routine laboratory tests are not specific.¹²

Intracranial HPCs can show very similar features to meningioma on both CT and MRI. They often presents as an extraaxial, multilobulated mass. They can have a narrow or a broad base of dural attachment. Unlike meningiomas, which frequently show hyperostosis of adjacent bone and may have intratumoral calcifications on unenhanced CT scans, HPCs show bone erosion and lack calcifications and hyperostosis. Unenhanced CT scans of hemangiopericytomas typically show hyperdense heterogeneous tumors, and T1-weighted and T2-weighted MR images typically show heterogeneous isointense tumors. On contrast-enhanced CT scans and MR images, HPCs show a heterogeneous enhancement.¹³ HPCs also shows marked vascularity similar to meningioma on angiography. A recent retrospective analysis concluded that tumors presenting outside the brain parenchyma, with isointense to slightly intense regions on MRI scans, oval/lobular shape, well- or ill-defined margins, signal-void vessels, apparent cystic areas, dual blood supply, and intense enhancement on CT or MRI scans, but without calcification or a “dural tail” sign, may be diagnosed as HPCs.¹⁴ PET-CT could be useful in differentiating the two entities, showing avid enhancement on CT but low FDG uptake on PET, indicative of low glucose utilisation.¹⁵ Some investigators have reported also the potential role of multitracers (F-FDG, Cmethionine, and O-H₂O) PET imaging or dual-tracer (C-acetate and F-FDG) PET/CT imaging or ¹¹¹In-pentetreotide scan in distinguishing intracranial HPC from meningioma.^{16,17} PET-CT is useful in the diagnostic pathway both to distinguish HPC from meningiomas but also to find distant metastases undetected by simple CT.

Immuno-histochemical study in addition to routine histopathological examination is essential to differentiate intracranial HPCs from angiomatous/anaplastic meningiomas and solitary fibrous tumor.¹⁸ Compared with MNG, MHCPs showed strong vimentine (100% of cases), CD99 (62%), bcl-2 (87%), and p16 (75%) staining but only focal positivity with EMA (33%) and NSE (37%).¹⁹

Radiation therapy options

The treatment for intracranial hemangiopericytomas is primarily total surgical resection of the lesion whenever possible. It correlates with the free interval of recurrence and overall survival.^{20,21,22,23} Pre-surgical embolization should be considered to reduce the risk of bleeding heavily during operation.^{24,25} Neoadjuvant radiotherapy has been also advocated to reduce intraoperative complications.^{26,27,28}

However, a complete surgical resection does not eliminate the high risk of local recurrences that occur in the central nervous system, often in the same surgical bed. The extension of surgical resection is very important: a large series has demonstrated a survival ratio of 10 years through 69% of those who underwent a gross total resection, compared to 44% of those who obtained a subtotal resection.⁷ The high propensity to local recurrence suggests a role for postoperative Radiotherapy. Sheehan *et al.* reported a decrease in local recurrences from 88% with surgery alone to 12.5% with surgery and postoperative RT.⁴² Recently, Kim *et al.* performed adjuvant RT (50 to 60 Gy) regardless of the extent of resection and pathologic grade in most of the patients and showed that the patients who received adjuvant RT tend to have longer RFS without significant radiation-related complications.²⁹ However, treatment with adjuvant radiotherapy even in cases of complete resection remains controversial. Many data have been published, but they often originate in small samples of retrospective studies and have conflicting results. Some studies found a improved recurrence-free survival with post-operative RT^{9,30,31,32,33} allowing protection also against tumor metastasis in neuraxis via cerebrospinal fluid but without impact on extra-CNS distant metastases. A recent review over 52 patients showed that postoperative RT significantly lengthened both local control (5 year LC rates of 97 vs 44%) and overall survival (10 year OS rates of 83 and 25%) independent of the extent of resection, without a preventive effects on regional and distant metastases. The main patterns of failure were local recurrence in patients who did not receive PORT and distant metastasis in those who received PORT.³⁴ Other studies showed no benefit in the addition of radiotherapy after a total resection when compared to gross total resection alone, and total dose >50 Gy was associated with increased mortality rates; postoperative radiotherapy offered no survival benefit also in cases of subtotal resection.²⁰ A recent retrospective review of 43 cases showed that postoperative radiation therapy may be able to prolong the time before first recurrence (p=0.04), but it does not confers a survival benefit (p=0.2).³⁵ The most common dose of postoperative RT is 45- 50 Gy.^{36,37} In case of residual or recurrent small-sized meningeal HPC, radiotherapy and in particular stereotactic radiosurgery (SRS) seems to be an effective treatment with excellent results. An analysis of high-precision RT (SRS or fractionated IMRT for more complex targets) for patients with intracranial HPCs demonstrates that high overall survival rates (100% and 64% at 5 and 10 years, respectively) can be obtained in patients by combining surgical and RT approaches. The main advantage of high-precision RT is the possibility of delivering high doses to more complex target volumes and sparing organs at risk, helping to improve local tumor control and preserving the patient's quality of life.³⁸ Also Gamma Knife radiosurgery is a feasible and effective therapy in the management of HPCs.³⁹ Meningeal HPCs can recur locally or distantly in the neural axis or as distant extraneural metastases. The recurrence and metastasis rates of intracranial HPC were reported to be 80% and 23%, respectively, and the 5-year metastasis rate is approximately 33%.⁴⁰ The incidence of extraneural metastases of M-HPC ranges from 12%¹ to 57%.⁴¹ Metastases occurred 2- 20 years after the initial

Table 1. Papers reporting cases of intracranial HPC that developed bone metastases.

Author	N pts	Metastases (%)	Site of metastases	Time to met (median)	Treatment of bone	Outcome metastases
Goellner, 1978	26	23	Retroperitoneum, liver, lung, bones	8.6 yrs	Unavailable	Unavailable
Anderson, 1980	1	100	Bones	5 yrs	Surgery + RT (femur) RT CHT	Slowly progressive disease at 3 yrs
Jaaskelainen, 1985	21	14	Bones, liver, pleura, lung, subcutis	6,4 yrs	Unavailable	Slowly progressive disease at 6,5 yrs
Staples, 1990	15	53	Bones, lung, subcutaneous tissue, massive intradominal disease	3 yrs	RT (26-30 Gy, 10-13 fr)	NED after 11 yrs
Sakata, 1998	1	100	Bones	20 yrs after the first treatment	RT (60 Gy in 24 fr over 5 weeks, 39 Gy in 13 fr over 3 weeks, 20 Gy in 4 fr over 2 weeks) + CHT	Partial response and no regrowth; good palliation
Dufour, 2001	21	19	Bones, lung	12 yrs	Unavailable	Slowly progressive disease at 4 yrs
Someya, 2001	4	50	Bones liver, lung, brain	7.5 yrs	RT bone 1: 25 Gy in 5 fr, 50 Gy in 16 fr S→ RT: 37.5 Gy in 15 fr RT bone 2: 25 Gy in 5 fr RT bone 3: 35 Gy in 8 fr	Death after 9 years
Suzuki, 2002	1	100	Pancreas, bones	22 yrs	RT	SD at 2 yrs
Ecker, 2003	38	29	Spine, chest wall, liver, pelvis, lungs, orbit, femur, deltoid, breast, humerus	Unavailable	Radiosurgical tratment and salvage chemotherapy treatment	5 yrs survival rate 93%
Kim, 2003	31	12.9	Liver, lung bones	8.9 yrs	Unavailable	Unavailable
Souyer, 2004	29	55	Lung, bone, liver, spinal	97 months	Gross total resection or subtotal resection + or - RT	The 5, 10 and 15-year overall survival rates 85%, 68% and 22%
Pistolesi, 2004	1	100	Bones, Adrenal glands	12 yrs	Surgery (femur) RT (30 Gy in 10 fractions) (vertebra)	NR
Chang, 2004	1	100	Bones, liver	5 yrs	RT 43.2 Gy	PD at 1 yr
Hoshi, 2005	15	100	Bones	>10 yrs	RT, S	Unavailable
Fountas, 2006	11	36.4	Bones, liver, lung	4.9 yrs	Unavailable	All dead
Purandare, 2010	1	100	Bones	8 yrs	RT (dse not specified)	SD at few months
Bassiouni, 2007	12	17	Unavailable	Unavailable	Unavailable	Unavailable
Ywamuro, 2008	1	100	Bones, liver	9 yrs	S	SD at 5 years
Ambrosini- Spaltro, 2010	1	100	Hip	13 yrs	Unavailable	Unavailable
Schiariti, 2011	39	26	Lung, bones, liver, muscle	75 months after their initial surgery	Surgical excision and EBRT when radical excision no possible and/ or chemotherapy	Overall survival rates at 5, 0, 15, and 20 yrs 93%, 1 67%, 45% and 23%
Rutkoski, 2012	35	20	Liver, skin, bone lung	Unavailable	Unavailable	4/7 died
Siegel, 2012	1	100	Bones	13 yrs	S (wide resection)	NED at 7 yrs
Kumar, 2012	15	7	Bones	5 yrs	RT (dose not specified)	Unavailable
Ghia, 2013	63	33	Unavailable	10 yrs	RT	Unavailable
Stessin, 2013	76	Unavailable	Unavailable	Unavailable	Total resection or Subtotalresection + RT	Unavailable
Satayasoonorn, 2014	4	100	Bones	7 yrs	Unavailable	Unavailable
Manatakis, 2015	1	100	Bone, liver	12 yrs	SRS	Unavailable
Nakada, 2015	2	100	Bones	8 yrs	Unavailable	Unavailable
Yamazaky, 2016 months	1	100	Rib	2 yrs	S	PD (multiple bone met) after 6
Wei, 2015	1	100	Bones, kidneys	4 yrs	C (bevacizumab + temozolomide) + RT (40 Gy in 10 fr)	Stable disease

diagnosis, and the average time-to-metastasis varied from 63 to 99 months.⁴² A systematic review over 523 patients showed a median time-to-metastasis of 91 months after primary surgical resection.⁴³ Galanis *et al.*⁴⁰ noted that bone and liver were the most common metastatic sites (82% and 41% of extraneural recurrences, respectively), while Brunori *et al.*⁴⁴ reported that the preferential sites were lung, bone, soft tissue, and liver. In a review of 94 cases published in 1991, the most common sites of metastases have been bone, lung, abdominal cavity, lymph nodes, skeletal muscle, kidney, pancreas and skin.⁷ A series of risk factors relevant to hematogenous dissemination capacity have been postulated, including subtotal resection of the tumor, development of local recurrence, large tumor size, and the tumor site (ex. proximity to venous sinuses).⁴⁵ Local or distant recurrence is often a late event,⁴⁶ and the probability of developing distant metastases increases steadily with time.⁴⁷ Kim *et al.* showed that extraneural metastases developed at an average of 107 months after the first operation, with 5- and 10-year metastasis rates of 4.4% and 24.9%, respectively.⁴⁸ Brunori *et al.*⁴⁴ reported that the mean interval to first recurrence was 84 months, Guthrie *et al.*²¹ and Goellner *et al.*⁴⁹ showed the recurrence rate at 10 years and 15 years after surgery, respectively, was 76%. In the series reported by Kim *et al.*⁴⁸ the overall average period before the first recurrence was 104 months. All these studies suggest the need of a close follow-up for a long period after the first surgical removal, that should include complete physical examination, chest X-rays, abdominal ultrasound, and total body CT or PET/TC, when indicated.

Table 1 reports a series of papers reporting cases of intracranial HPC that developed bone metastases. The median time-to-metastases was 8 years (range 2-22 yrs). Bone metastases were treated with surgery, chemotherapy or palliative Radiotherapy or a combination of treatment modality. RT doses are not always reported: they ranged from 25 to 50 Gy, given often with a hypofractionated modality. A strategy of optimal systemic treatment of metastatic HPC has not yet been identified, being the role of anthracyclines-based chemotherapy still controversial due to its modest efficacy in this setting of patients.^{50,51} The recent identification of the fusion gene NAB2-STAT6 both in HPC and in solitary fibrous tumors^{52,53} shows a new area of research. The overexpression of the Vascular Endothelial Growth Factor Receptor (VEGFR) and Platelet-Derived Growth Factor Receptor (PDGFR) encourages the study of targeted therapies with antiangiogenic drugs.^{54,55,56,57,58} Park *et al.* analyzed the records of 14 patients with HPC/SFT treated with temozolomide and bevacizumab: 79% of patients achieved a partial response, 14% had stable disease only 1 patient had progressive disease, concluding that this generally well-tolerated combination therapy is clinically beneficial.⁵¹ Despite the tumor's natural tendency to recur and metastatize outside the CNS, it is possible to ensure a long survival time and a good quality of life. Palliative radiation of painful bone lesions has been reported to control pain successfully. Doses of 30 Gy/10 fractions. The long-term benefit of wide resection of a solitary metastatic bone lesion is not well known. Staples *et al.* showed that pain due to bone metastases was palliated by 12 Gy in 4 fractions and 30 Gy in 15 fractions.⁵⁹ Friedmand and Egan recommend a dose up to 30 Gy over 18 days,⁶⁰ while Sakata *et al.* reported both a pain relief and a prevention of pathological fractures with doses up to 20-60 Gy in 4-24 fractions.⁶¹ Palliative therapy with irradiation of bone metastases could provide good local control and maintain the patients' quality of life.

Conclusions

RT seems to carve out a significant role in the treatment of

such a complex and extremely rare disease.

The available literature reveals no consensus about the radiation dose to be used for the locoregional control of HPC. Treatment with adjuvant radiotherapy even in cases of complete resection remains controversial. Many data have been published, but they often originate in small samples of retrospective studies and have conflicting results. So, further studies are needed.

Our experience confirms data of literature: even after gross total resection, we observed a long time-to-metastases (5 years) and an overall mean survival of 8 years. Palliative RT conducted with 30 Gy in 10 fractions over two weeks was effective both in slowing down disease progression and in giving pain relief of the metastatic bone allowing a good quality of life. Actually, no doubt evidence is all in favor of RT obtaining local pain control with good tolerance and better quality of life at least at one-year-follow up.

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