Conventional Hemangiopericytoma

Modern Analysis of Outcome

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BACKGROUND. Hemangiopericytoma (HPC) is a rare vascular tumor, and pathologic distinction from synovial sarcoma and solitary fibrous tumor is a significant problem due to shared histologic features. In the current report the authors defined the clinical behavior and prognosis for patients with HPC.

METHODS. Between July 1982 and February 1998, 62 patients with a diagnosis of primary, recurrent, or metastatic HPC were identified from a prospectively maintained database. The pathology of all cases for which material was available (57 cases) was re-reviewed for histologic confirmation of the HPC diagnosis. Using strict pathologic criteria, including immunohistochemistry and electron microscopy, tumors from 25 of 57 patients qualified for the diagnosis of conventional hemangiopericytoma; those tumors formed the basis of the current report. Survival was determined by the Kaplan-Meier method.

RESULTS. At the time of initial presentation, 19 patients had primary tumors, 3 had locally recurrent disease, and 3 had metastatic disease. The most frequent anatomic sites for HPC were the extremities, the pelvis, and the head and neck, accounting for 80% of the total cases. The median followup (n = 25) was 49 months (range, 1 to 160 months). The two and five year overall survival rates (n = 25) were 93% and 86% respectively. The disease-specific survival was 86% at last followup. Patients undergoing complete resection (n = 16) showed a 100% median survival at 60 months.

CONCLUSIONS. At present, complete tumor resection for patients with conventional HPC is recommended. However, considering the favorable outcome in this disease, the authors caution against performing operations that may potentially cause loss of function or are limb threatening.

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Among vascular tumors, the diagnosis of hemangiopericytoma (HPC) is one of the most controversial. Doubt has even been raised as to its existence as a specific tumor type.¹ Initially described by Stout and Murray in 1942,² HPC was thought to represent a neoplasm of the pericytes of Zimmerman. Hemangiopericytoma is included in an authoritative classification of soft tissue tumors,³ but it is likely over-diagnosed. Histologic confusion with other soft tissue tumors, such as solitary fibrous tumor (SFT) and synovial sarcoma, is a significant problem, due to a shared hemangiopericytoma-like vascularity of all three tumors.⁴,⁵ Prior to the routine use of immunohistochemistry in the diagnosis of HPC, misinterpretation for synovial sarcoma was common. However, unlike HPC, synovial sarcomas are
often immunoreactive for both keratins and epithelial membrane antigen (EMA). Electron microscopy is also helpful in separating the two tumors, as epithelial differentiation is identified in some synovial sarcomas studied ultrastructurally but not in examples of HPC. Basement membrane substance may be found in both HPCs and synovial sarcomas. Yet it is the presence of basement membrane in HPCs that allows distinction from SFT, a tumor of fibroblasts, composed of cells devoid of a basement membrane lining. Additional evidence for determining whether a hemangiopericytoma-like tumor is a synovial sarcoma is available by genetic studies. Over 80% of synovial sarcomas have a specific rearrangement t(x;18)(p11.2; q11.2), demonstrable by cytogenetics, fluorescence in-situ hybridization, and molecular genetics using a reverse transcriptase-polymerase chain reaction looking for the SYT-SSX1 or SYT-SSX2 fusion transcripts. However, identifying the presence of such a chromosomal translocation in either wet tissue or paraffin material requires highly specialized techniques that are not available in most pathology laboratories.

The current study is an analysis of patients with conventional HPC identified from a larger group of patients with a database-coded initial diagnosis of HPC made over a period of almost 16 years. Patients included in the current analysis had their diagnoses confirmed in a pathologic reassessment using what is now routine immunohistochemistry and, in about half the cases, electron microscopy. The study does not include any examples of a recently described variant of HPC, designated lipomatous hemangiopericytoma, which has a mixed histology of mature fat and hemangiopericytoma; followup has thus far shown the tumors to be benign. Also excluded from the current study are tumors considered by others to be glomangiopericytoma or myopericytoma.

MATERIALS AND METHODS
A prospective database of adult patients (older than 16 years) with soft tissue sarcoma, treated at the Memorial Sloan-Kettering Cancer Center, was established in July 1982. From this database 62 patients who underwent treatment for the diagnosis of HPC rendered between July 1982 and February 1998 were identified.

Pathologic material was available for reassessment in 57 cases. Three experienced soft tissue sarcoma pathologists (J.M.W., C.A., J.S.) independently reviewed all specimens, and only those cases which had a conventional HPC appearance on hematoxylin and eosin-stained sections and for which there was unanimous agreement about the classification were included in the current analysis. Pathologic material consisted of histologic slides, paraffin blocks on which immunohistochemistry was performed (in many cases stained for the first time because the cases antedated in time the common use of this technique), and electron photomicrographs (in 25 cases). Neoplasms reactive for keratins or EMA were considered synovial sarcomas or possible synovial sarcomas and excluded. Any neoplasm failing to show basement membrane material if examined ultrastructurally and having cells with prominent rough endoplasmic reticulum typical of a fibroblastic neoplasm were also not included. Tumor evaluation did not include genetic analysis to rule out synovial sarcoma.

For those tumors where there was unanimous agreement that conventional HPC was the appropriate diagnosis, operation, clinical, and pathologic variables were obtained from the database and correlated with survival endpoints. Clinical variables analyzed included site, age at diagnosis (< or > 50 years), and gender. Operation variables analyzed were gross and microscopic margins (negative or positive). Tumor variables analyzed were size (≤ 5, > 5 to ≤ 10, and > 10 cm).

Survival and Statistical Analysis
Disease-free and disease-specific survivals were calculated utilizing the method described by Kaplan and Meier. Due to the small number of patients and events in the current study, only descriptive statistics are presented.

RESULTS
Patients
From the re-review of 57 patients with available pathologic material, 19 had sarcomas of uncertain type, 6 had monophasic synovial sarcomas, 4 had histologically benign solitary fibrous tumors, 3 had angiosarcomas, and 25 had what was unanimously considered to be conventional HPC (Table 1).

In the conventional HPC group (n = 25), 16 patients (64%) were < 50 years of age. At the time of initial presentation, 19 patients (76%) had primary tumors, 3 (12%) had locally recurrent disease, and 3 (12%) had metastatic disease.

Tumor Site
The most frequent anatomic tumor sites were the extremities in 7 patients (28%), the pelvis in 7 patients (28%), and head and neck in 6 patients (24%). Extremity tumors were mostly in the axilla and thigh, and there were two meningeal and two cheek tumors in the head and neck group.
All tumors were deep rather than superficial in location. Seven tumors were < 5 cm, 10 ranged from 5-10 cm, and 7 were larger than 10 cm in size.

**Followup**
The median followup interval for all patients (n = 25) was 49 months (range, 1–160 months).

**Recurrence**
Following resection, only one patient subsequently developed local recurrence, and this patient had an initial metastatic disease presentation.

**Metastasis**
Following resection, five patients subsequently developed metastases, three of which occurred in patients presenting with primary lesions. In the locally recurrent and metastatic disease presentation groups, one patient in each developed metastases. Overall metastasis-free survival (M-FS) was 69% at last followup. Patients with primary tumors at presentation had an 80% M-FS at five years while those with recurrent disease at presentation had a 55% M-FS at five years.

**Survival**
The two- and five-year overall survivals (Fig. 1) for patients with HPC (n = 25) were 93% and 86%, respectively; at last followup, 22 patients were alive and 3 were dead of disease (DOD). For patients DOD, none had presented with a primary tumor, two had a local recurrence, and one presented with metastasis.

Conversely, patients originally included as HPC and subsequently excluded by conventional HPC criteria showed a tendency for worse overall survival outcome, although statistical analysis was precluded by the varied diagnoses and small size of the cohort. However, excluding the cases of benign solitary fibrous tumor (n = 4), at the time of the current analysis, for patients composing the residual excluded 28 cases, 15 out of 28 (54%) were DOD.

At the time of writing, grouped by description and by diagnosis, of the 19 patients diagnosed as sarcoma of uncertain type, 9 were DOD, 2 were dead of unknown cause (DUK), 2 were dead of other causes (DOC), and only 4 remained with no evidence of disease (NED). Of the six cases re-examined and diagnosed as synovial sarcoma, two were DOD, one was DUK, and three were NED. Angiosarcoma was diagnosed in three other cases; two were DOD and one remained alive with disease at the time of the current analysis.

**Prognostic Factors**
Analysis of prognostic factors inclusive of neoadjuvant/adjuvant therapies was precluded by the modest size of the patient group.

**DISCUSSION**
Hemangiopericytoma assumes two histologic forms, conventional HPC and the lipomatous HPC variant. Both histologic forms share a sponge-like sinusoidal vasculature and staghorn-shaped blood vessels that are haphazardly bounded and surrounded by ovoid and short spindle shaped cells. On ultrastructural analysis the cells are largely undifferentiated, containing arrays of intermediate filaments consistent with vimentin. If ultrastructural confirmation is sought, a necessary feature is the presence of the basement membrane substance between tumor cells.
Histologic identification of lipomatous HPC is readily achieved because of an HPC- or SFT-like appearance with the added finding of a lipomatous component. Of the 19 lipomatous HPCs that have been reported thus far, following resection only one patient experienced local tumor recurrence, and none have developed metastases. In support of that, conservative clinical management is the appropriate treatment for the lipomatous HPC variant.

Conventional HPC, described by Stout and Murray in 1942, does not lend itself to such ready histologic identification. Enzinger and Smith’s 1976 paper on HPC warned of several tumor types with which HPC may be confused by virtue of a similar vascularity featuring staghorn shaped blood vessels. The tumor they noted which most closely resembled HPC was synovial sarcoma. In recent years, histologic distinction from SFT has proven equally problematic. Basing their diagnosis on routine histology and reticulin-stained material, Enzinger and Smith recognized 106 HPCs. In their series, followup information was available for 93 of 106 patients, of whom 14% had died of disease. Their reported 10-year-survival rate was 70%. Two other studies of conventional HPC, conducted before the routine use of immunohistochemical techniques to identify cell types of soft tissue sarcomas, are revealing. In an evaluation of 60 patients, McMaster et al. found that 48% had died of disease. Of the 19 patients reported by Auguste et al., 53% developed pulmonary metastases; the overall survivals were 59% and 47% at 5 and 10 years, respectively. Such a wide spread in reported outcome suggests a lack of uniform pathologic criteria in these studies.

Expectation that immunohistochemistry would help identify neoplastic pericytes and thus permit direct recognition of HPC has met with limited success. Cell markers focally present in normal pericytes, such as desmin and muscle actins, are infrequently found in neoplastic cells of HPC. Although usually immunohistochemically mute for muscle markers, greater success has been reported using antibodies to factor XIIIa and CD34. Findings with regard to factor XIIIa have yet to be confirmed, while the diagnostic usefulness of CD34 is negated by its more consistent and stronger staining of SFT, an HPC look alike.

Until now, immunohistochemistry has been used primarily to exclude tumors histologically simulating HPC. The tumor of greatest clinical concern in this respect is the monophasic form of synovial sarcoma. Approximately two thirds of primary monophasic synovial sarcomas immunostain for keratins and/or EMA; however, HPC usually does not express EMA and has not been reported to stain for keratins. Therefore, in the current study, any HPC-like tumors reactive for keratins or EMA were regarded as a probable or possible synovial sarcoma and excluded. The cells of both HPC and synovial sarcoma may form a basement membrane, so its presence when seen was used either to confirm the possibility that the tumor was an HPC or to rule out an SFT.

Hemangiopericytoma is principally a tumor of adult patients, and, in current series, the median patient age was 45 years. The most common anatomic locations for lesions in the current study, the extremities, the pelvis, and the head and neck, occurred with similar frequency. These sites are similar to those reported in the literature for conventional HPC.

Clinical presentation of conventional HPC is nonspecific. Pain is a late symptom associated with an enlarging mass; however, the symptom complex varies depending on the site of disease. Characteristically, HPC is a well-circumscribed, brown, spongiiform lesion, surrounded by a pseudo-capsule, often with small satellite nodules separate from the main tumor mass. In contrast, synovial sarcoma is grossly cream-colored, while SFT is gray on gross examination. The presence of tumor extension beyond the principal tumor mass has also been described for other types of soft tissue sarcomas.26,27

In the largest reported series to date, HPC occurred in 17% of the cases. Our experience is that conventional HPC has two- and five year overall survival rates of 93% and 86%, respectively. These are clearly divergent survival data as compared to those previously reported. We believe that this substantial difference in survival is due to our use of immunohistochemistry and electron microscopy in a multimodal pathologic review to exclude other soft tissue tumors histologically mimicking conventional HPC. The vastly different experience of improved overall survival for this cohort as compared to the literature is an important observation.

The > 50% mortality showed over the same interval by patient cases determined on re-examination to be other than conventional HPC underscores the importance of applying strict diagnostic criteria in making the most appropriate diagnosis.

Similar to the favorable overall survival showed in the current report, a five-year disease-specific survival of 86% and an overall metastasis-free survival of 69% were observed. For patients presenting with primary tumors (n = 19), disease-specific survival at five years was 100%. Furthermore, patients who underwent complete tumor resection (n = 16) also showed a 100% survival at five years.
Although this analysis examined a modest cohort, it is important to note that of the 25 patients initially identified and included in this analysis, 22 were alive at the time of writing, with a median followup of 49 months. These results strongly suggest a more favorable survival outcome for patients with HPC than what has been previously reported. In contrast, had histologic re-examination not been performed on the current series of cases spanning a 16 year interval, the results of the current study would have paralleled previous reports in the literature, which in the best analysis would have included 18 patients (3 conventional HPC and 15 excluded cases) of the total 57 cases reviewed as DOD.

Conventional HPC is capable of both local recurrence (1 of 25 patients, 4%) and distant metastasis (5 of 25 patients, 20%) but has a low disease associated mortality. Of patients developing metastases, three of five had presented with primary tumors. The other two patients progressing to metastatic disease included one patient presenting with locally recurrent tumor and one patient presenting with metastatic disease. The single patient who developed local recurrence had presented with metastatic disease. The capacity for malignant behavior of conventional HPC further distinguishes this tumor from the thus far benign lipomatous HPC variant.

CONCLUSIONS

At present, we favor surgical resection for patients with conventional HPC. Furthermore, we recommend the extra effort to confirm the diagnosis of conventional HPC prior to initiating surgical treatment. Considering the favorable prognosis of conventional HPC observed in the current analysis, we underscore the importance of the appropriate diagnosis before operations with a potential for loss of function are performed in these patients.

Future reports on an expanded cohort of patients, with a diagnosis of HPC established by a multimodal pathologic evaluation, would be useful in further defining the natural history of this disease and may potentially identify prognostic outcome factors. However, answering these and other questions will be a challenging endeavor, given that HPC is an uncommon soft tissue tumor.

REFERENCES


