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SARCOMAS (SR PATEL, SECTION EDITOR)

Vascular Sarcomas

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Abstract Vascular sarcomas are soft-tissue tumors that arise from the endothelium with a malignant potential. This review discusses the management of epithelioid hemangioendothelioma (EHE) and angiosarcoma. EHE is a vascular tumor of intermediate malignant potential with an indolent course. EHE arising from the liver, lung, or bone tends to be multifocal and the rate of progression is slow and often unpredictable. Treatment should be considered in patients with significant symptomatic deterioration and/or progressive disease on imaging studies. Various cytotoxic and targeted therapies are available for management, with disease stabilization as the most common outcome. Angiosarcoma is an aggressive vascular tumor with a high malignant potential. Multidisciplinary care is critical for the management of localized disease, and the best outcomes are often observed in patients when a combination of systemic and local therapy options is used. Metastatic angiosarcoma is treated primarily with systemic therapy, and several cytotoxic and targeted therapies are available, alone or in combination. The choice of therapy depends on several factors, such as cutaneous location of the tumor, performance status of the patient, toxicity of the treatment, and patient goals.

Keywords Epithelioid hemangioendothelioma · Angiosarcoma · Vascular tumors · Vascular sarcomas · Vascular sarcoma · Angiosarcoma treatment · Bevacizumab · Sorafenib · Sunitinib · Orally administered cyclophosphamide · Pazopanib · Paclitaxel · Gemcitabine · Docetaxel · Adriamycin · Doxorubicin · Ifosfamide

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Introduction

Vascular sarcomas arise from blood vessels and can range from benign neoplasms with no metastatic potential such as hemangiomas to angiosarcomas, with an extremely high propensity for local recurrence and metastasis. Vascular tumors may be classified as shown in Table 1. Hemangiomas closely resemble normal blood vessels and can be hard to differentiate from hamartomas or malformations. These may be localized or diffuse, involving a large segment of the body. There is no evidence to suggest that they undergo malignant transformation. At the other end of the spectrum are angiosarcomas, which are clearly malignant and have an aggressive clinical course. Between these extremes are neoplasms of intermediate malignant potential, such as epithelioid hemangioendotheliomas (EHEs), which can establish metastatic disease but have an indolent clinical course spanning several years. For the purpose of this review, we will focus on vascular tumors with malignant potential.

Hemangioendothelioma

Hemangioendotheliomas are vascular tumors of intermediate malignancy that have the potential to recur or metastasize, but at a much lower rate than conventional angiosarcomas. EHE is probably the most aggressive member of the group (see Table 1), with the highest potential for metastasis.

Epithelioid Hemangioendothelioma

Clinical Features

This angiocentric vascular tumor can occur at any age and is often closely associated with a blood vessel, usually a medium-sized or large vein. EHE can occur in the soft

Table 1 Classification of tumors of vascular origin

Benign vascular tumors	Vascular tumors of intermediate malignancy	Malignant vascular tumors
Localized hemangiomas	Epithelioid hemangioendothelioma	Angiosarcoma
Capillary hemangioma	Spindle cell hemangioendothelioma	Kaposi's sarcoma
Cavernous hemangioma	Malignant endovascular papillary angioendothelioma	
Venous hemangioma		
Arteriovenous hemangioma		
Epithelioid hemangioma		
Hemangioma of granulation tissue type		
Miscellaneous hemangiomas of deep soft tissue		
Angiomatosis		

tissues [1, 2], bone [3], liver [4], and lung. EHE of soft tissues is evenly distributed between males and females, whereas EHE of the liver and lung occurs more commonly in females and tends to be multifocal [5] with extensive growth along small vessels [6]. Symptoms are nonspecific; presentation with a painful or tender mass is common in soft tissues. In other sites, the symptoms are dependent on the location. Tumor can also be asymptomatic, especially in the liver, where it may be an incidental finding in as many as 42 % of patients [4]. Right upper quadrant pain is described by one third of symptomatic patients when the liver is involved. Other symptoms include fatigue, anorexia, nausea, and poor exercise tolerance. Patients are usually symptomatic for 3 months to 2 years prior to diagnosis. Physical examination findings may be normal in many patients but can show jaundice, hepatomegaly, palpable masses, ascites, and right upper quadrant and epigastric tenderness.

Pathologic Diagnosis

Biopsy is required to establish the diagnosis, and owing to the solid growth pattern and epithelioid appearance, this tumor may be mistaken for a metastatic carcinoma. EHEs occurring in other sites such as bone, lung, or liver are even more likely to be confused with carcinoma. In fact, in the lung, they were initially thought be an intravascular variant of bronchioloalveolar carcinoma, with subsequent identification of their endothelial origin [7]. EHE can be distinguished from a carcinoma by the lack of pleomorphism and mitotic activity and the presence of focal vascular channels [1]. Pathology review at a high-volume sarcoma center is strongly recommended prior to establishing diagnosis.

Clinical Behavior and Prognosis

EHE is a tumor with intermediate malignant potential capable of both local recurrence and establishing metastatic disease but at a much lower rate compared with angiosarcoma. Local recurrence occurs in about 12–13 % [1, 2] of patients with EHE of the soft tissues. Bone, liver, and lung EHEs are often multifocal at diagnosis and may not be resectable when finally diagnosed.

Prognosis of EHE is variable and often unpredictable. In about one third of patients with EHE, EHE can metastasize (range 21-31 %), and mortality ranges from 13 % in EHE of soft tissues to 31 % in EHE of bone and 43 % in EHE of the liver [1–4]. The presence of metastasis does not consistently affect prognosis, and patients with metastatic disease can survive for a long time [8, 9]. Not all patients with metastasis die of their disease; among patients with metastatic EHE of the liver, the mortality rate was reported to be 63 % [4], and among patients with metastatic EHE of the soft tissues, less than half of the patients died of their disease. This is because half of all metastasis are in the regional lymph nodes, and the excision of these structures may result in cure or at least long-term disease-free survival [6]. Certain pathologic features of EHE have been associated with poor outcomes and rapid progression. These include marked cellular atypia [2], more than one mitosis per ten high-power fields [1, 2], necrosis [1], extensive spindling [1], or solid areas of overt angiosarcoma [6].

Treatment of EHE

Soft-Tissue EHE

Isolated soft-tissue tumors should be treated with curative resection with adequate margins. Because of the 13 % local recurrence risk [1], preoperative/postoperative radiation therapy should be considered in patients where good margins are not possible or could not be established.

Since half of patients with metastasis develop nodal metastasis, they must be considered for re-excision, which may result in long-term disease-free survival. In other patients with truly multifocal disease, no intervention is suggested until the biological behavior is assessed with close follow-up (CT every 3 months). If definitive

progression is noted on imaging studies, these patients may be considered for treatment with antiangiogenic therapy or conventional chemotherapy (see "Systemic Therapy for EHE").

Hepatic EHE

For disease localized to the liver, resection may seem to be a potentially curative treatment; however, multifocal involvement can occur in as many as 87 % of patients [5] and limits the utility of liver resection. There are also concerns of liver resection promoting the growth of EHE through hepatotropic growth factors, but this is based on data limited by small numbers [10].

Liver transplantation has been reported to be the most commonly studied modality in the management of hepatic EHE [5]. Five-year survival rates of 48 % [11], 43 % [12], 55 % [13], and 71.3 % [14] have been reported with liver transplantation in small case series. Even though conceptually this therapy may appear attractive, the prevalence of extrahepatic disease is fairly common, and disease-free survival continues to be poor. Even in the study that reported the highest 5-year survival rate, the disease-free survival rate at 5 years was only 60.2 % [14]. Patients who undergo liver transplantation are likely to be at an earlier stage in the natural history of EHE and tend to have better 5-year survival, and comparisons with medical therapy (which is usually used in the treatment of patients with more advanced stage disease) should be made with caution. Because of the mediocre disease-free survival, lead-time bias, and comparable outcomes with non-transplant-based approaches, at our institution liver transplantation is not favored for this disease.

Systemic therapy options have been explored but have been poorly studied in hepatic EHE. Both cytotoxic chemotherapy and targeted therapy have been attempted in the treatment of EHE (see "Systemic Therapy for EHE").

Bone EHE

EHE can occur in the bone, and is most often multifocal (55 % [3]), with predominantly skeletal involvement. Visceral involvement seems to be the most important criterion in predicting the prognosis of EHE in the bone. In the Mayo Clinic series, radical resection, when possible, emerged as the treatment of choice [3]. Experience with chemotherapy is limited, and chemotherapy may be attempted in the setting of visceral involvement.

Systemic Therapy for EHE

Systemic therapy options have been poorly studied in EHE. Most of the information comes from small case reports. Among cytotoxic agents, intra-arterial chemotherapy with an emulsion of mitomycin and lipiodol [15], 5-fluorouracil (intra-arterial chemotherapy) [16], doxorubicin [17], and the combination of epirubicin and dacarbazine [18] have been tried, with variable results. Doxorubicin may have some benefit, but the efficacy of other agents is uncertain and requires more study. Systemic therapy with antiangiogenic agents also appears to hold some promise. In a phase II trial of bevacizumab in patients with EHE that enrolled seven patients, two partial responses (29 %), four patients with stable disease (57 %), and one patient with progressive disease (14 %) were observed [19]. Another phase II study, by the French Sarcoma Group using sorafenib (800 mg daily), enrolled 13 patients with progressive EHE to determine the 9-month progression-free rate. Four of 13 patients (30.7 %) remained without progression at 9 months. Two partial responses were observed in the trial, which lasted 2 months and 9 months [20•]. Interferon alfa-2b was shown to produce substantial regression in a patient with extrahepatic disease who underwent liver transplantation [21]. Other angiogenesis inhibitors with reported activity include thalidomide [22] and lenalidomide [23]. Lenalidomide has been reported to induce stability of disease in a patient for more than 6 years [23].

Choosing the optimal therapy for patients with EHE remains a challenge in the absence of good prospective clinical trials with a control arm. EHE can frequently have an indolent clinical course spanning several years, when the patient might remain asymptomatic, with the disease undergoing slow progression with periods of stable disease and in some rare cases even spontaneous regression [24]. The slow pace of growth of EHE with prolonged periods of stability even in the absence of any treatment makes it hard to interpret reports of clinical benefit without adequate controls.

Tumor growth rate, which may be very slow initially, is not uniform during the course of the illness and can escalate during the later stages. This nonuniformity in the rate of progression poses a problem when comparing treatments that are used at different stages of EHE. For example, surgical approaches such as liver transplant or liver resection may be performed on a patient who is in the early stages of EHE, whereas medical therapy options are often pursued in patients with progressive multifocal disease that occurs later in the course of the illness. Since the rate of growth is different in the two situations, comparing progression-free survival between two treatment modalities may not yield the true difference in efficacy and will reflect the differences in tumor biology.

Patients are often diagnosed with EHE at different stages of their disease; some are diagnosed incidentally in the asymptomatic stage owing to the widespread use of imaging studies in medicine today. Stability of disease seen in a patient who is in the early stages of the disease while receiving a particular therapy may not be due to the treatment but could be due to the inherent nature of the disease. Currently there is no consensus on when treatment should

be initiated in a patient and when the patient should be observed. At MD Anderson Cancer Center, we observe these patients off therapy until clear evidence of progressive disease is apparent in imaging studies or when symptomatic deterioration occurs. Medical therapy is often preferred as the disease is often multifocal.

Angiosarcoma

Angiosarcomas are extremely rare (less than 2 % of all sarcomas) but highly malignant mesenchymal neoplasms that show endothelial differentiation recapitulating many of the functional and morphological features of normal endothelium [25].

Etiopathogenesis

Chronic lymphedema and radiation exposure are the most well-recognized predisposing factors for the development of angiosarcomas. Chronic lymphedema of any origin can predispose to the development of angiosarcoma, and the occurrence of angiosarcoma in the setting of lymphedema is referred to as Stewart–Treves syndrome. Chronic lymphedema may be secondary to treatment for breast cancer or may be due to benign causes such as filariasis, Milroy's disease [26]. The exact mechanism by which chronic lymphedema produces angiosarcoma is uncertain. Growth and proliferation of blocked lymphatics and dysregulation of normal control mechanisms have been postulated as a possible mechanism. Other suggested mechanisms include lack of immunologic surveillance and the presence of carcinogens in the accumulated lymphatic fluid [25].

Radiation exposure is a well-documented predisposing factor in the development of angiosarcoma and is commonly observed in patients who undergo radiation therapy for breast cancer. In many cases, these patients also have coexistent lymphedema, making it difficult to dissect the relative contribution of each. However, true post-radiation-therapy angiosarcoma does occur in the absence of lymphedema in patients with breast cancer and other cancers such as Hodgkin's disease, endometrial cancer, and cervical cancer. The latency after exposure may be 10 years or more [25]. Other predisposing factors that might contribute to the development of angiosarcoma are immunosuppression following kidney [27–38] or liver [39] transplant, the presence of foreign material [40–49], and exposure to vinyl chloride, thorium dioxide, and arsenic. Angiosarcoma can occur in association with other diseases such as Maffucci syndrome [50, 51], retinoblastoma [52, 53], xeroderma pigmentosum [54–57], Klippel–Trénaunay–Weber syndrome [58], neurofibromatosis [59–66], and other neurogenic tumors [67–69].

Clinical Features

Angiosarcoma has a predilection for skin and superficial soft tissues, with almost 60 % of patients presenting with primary skin or superficial soft-tissue involvement. Other common locations of involvement include breast, liver, bone, spleen, and heart. Clinical behavior is dependent on the location of the disease, and will be discussed here accordingly. Cutaneous angiosarcoma can be associated with chronic lymphedema (see "Etiopathogenesis") or can occur in the absence of lymphedema, which is more common than the former.

Cutaneous angiosarcoma without lymphedema commonly occurs in the head and neck region, the scalp especially appears to be a favored site, contributing to 31–52 % [70, 71] of cases, followed by extremities and other sites. A typical history includes the development of a bruise-like area that does not resolve and continues to enlarge. Bleeding from these lesions is common and is often the most common reason to seek medical attention. Advanced lesions are elevated and nodular, with portions of the lesion ulcerated. Involvement is often multifocal, which leads to difficulty in clinically assessing the extent of the lesion and planning local therapy, resulting in high failure rates associated with initial local therapy.

Angiosarcoma associated with lymphedema most commonly occurs in women following mastectomy. Benign conditions such as filarial lymphedema and lymphedema due to congenital or traumatic reasons have also been reported to precede angiosarcoma in the extremities. The pathogenesis of lymphedema resulting in the development of angiosarcoma is poorly understood. Even though more than 90 % of all angiosarcomas associated with lymphedema occur in patients following mastectomy for breast cancer, only 0.45 % of all women who survive for 5 years or more develop angiosarcoma as a complication of lymphedema. Women who develop significant lymphedema after mastectomy during the first year are at increased risk, and angiosarcoma can develop within 10 years (range 4–27 years) [25]. Superficial lesions are nodular and easily palpable and can develop ulceration with a serosanguineous discharge. Deeper lesions may present with discoloration of the overlying skin.

Treatment of Angiosarcoma

Multidisciplinary care with consultation at a high-volume sarcoma center is strongly recommended owing to the rarity of angiosarcoma and the lack of randomized clinical trials to guide treatment.

Treatment of Localized Disease

Even in patients with localized angiosarcoma, multifocal involvement within the local area is very common. For this

reason, recurrence rates are often high, and multidisciplinary care produces better outcomes [72, 73] regardless of the location of the tumor. At our institution we prefer to treat patients with neoadjuvant chemotherapy followed by surgery and radiation therapy. Doxorubicin-based and taxane-based approaches both have excellent outcomes, and the choice of the regimen depends on the primary location of the disease, histological subtype, performance status of the patient, and potential for toxicity. For patients with cutaneous angiosarcoma, paclitaxel appears to have excellent outcomes and is a reasonable first choice owing to its favorable toxicity profile. For patients with noncutaneous angiosarcoma, combination chemotherapy with doxorubicin and ifosfamide is preferred. Use of combination chemotherapy with gemcitabine and docetaxel may be a viable option for patients with cardiac dysfunction who require neoadjuvant therapy. It is not unusual for patients to have an excellent response to initial neoadjuvant chemotherapy. Additional local therapy (with radiation and surgery) should be still pursued for optimal long-term survival. For example, among patients with head and neck angiosarcomas treated at MD Anderson Cancer Center, patients who received all three modalities of treatment had the best outcomes [73].

Treatment of Metastatic Disease

Systemic therapy forms the mainstay of treatment for patients with metastatic angiosarcoma. Although both single-agent and combination chemotherapy options are available for patients with metastatic disease, multiagent chemotherapy tends to have better response rates and durability compared with single-agent chemotherapy [70]. Since complete responses can occur in a subset of patients with metastatic disease, multiagent chemotherapy should be considered in a well-selected subset of patients on the basis of performance status, comorbidities, and most importantly, patient goals. The presence of metastasis in certain locations, such as the brain, liver, and bone, tends to result in a low likelihood of complete durable responses, and this should be considered while discussing prognosis and setting the goals of care with the patient.

Single-Agent Chemotherapy

Doxorubicin

Several case reports [74–77] and retrospective studies [70, 78, 79] have demonstrated the utility of doxorubicin [70, 78] and its pegylated liposomal formulation [70, 74–77, 79, 80] in the treatment of unresectable disease. The response rate among patients with angiosarcoma is 29.5 % [78] with doxorubicin and 33 % [79] with liposomal preparations. A similar proportion of patients develop stable disease. Complete responses are seen in 6 % [78] of patients with doxorubicin and occur infrequently with liposomal doxorubicin [75]. Progression-free survival ranges from 3 months [78] to 3.7 months [70] for doxorubicin and from 4.2 months [70] to 5 months [79] for liposomal doxorubicin. It is critical to remember that these estimates are obtained from retrospective studies with a small number of patients.

Paclitaxel

The activity of paclitaxel in patients with angiosarcoma was first observed in a phase II clinical trial of this agent in soft-tissue sarcomas where a patient with angiosarcoma had a complete response [81]. Subsequently, a group of nine patients with angiosarcoma of the head and neck were treated with paclitaxel, and eighth (89 %) of them developed a major response that lasted 5 months [82]. The ANGIOTAX study, a phase II trial that enrolled 30 patients with angiosarcoma receiving paclitaxel at 80 mg/m^2 (days 1, 8, and 15 of a 4-week cycle) showed a response rate of 18 % at 4 months, with a median time to progression of 4 months [83]. A retrospective review of 117 patients with metastatic angiosarcoma has shown that paclitaxel weekly may have efficacy comparable to that of doxorubicin as a single agent in patients with cutaneous angiosarcoma [78]. This study also showed that of the 68 patients treated with paclitaxel, 13 % had a complete response, 40 % had a partial response, and 29.5 % developed stable disease. Since paclitaxel has a favorable toxicity profile compared with doxorubicin, it is a preferred agent for cutaneous angiosarcoma.

Gemcitabine

Stacchiotti et al [84]. reported on the use of gemcitabine in 25 patients with angiosarcomas (22 of 25 patients had epithelioid angiosarcoma), where 8 % had a complete response, 56 % had a partial response, 8 % had stable disease, and 28 % developed progressive disease. The median time to progression was 7 months in this study. Fury et al [70]. reported on 11 patients treated with gemcitabine (mostly third line setting), where the median time to progression was 2.2 months. This difference is likely related to differences in drug administration and the number of prior therapies. Administration of gemcitabine on days 1, 8, and 15 of a 28-day cycle appears to have better outcomes than administration on days 1 and 8 of a 21-day cycle. Use of gemcitabine alone or in combination with taxanes is a viable option for patients with angiosarcoma, especially of the epithelioid subtype.

Vinorelbine

In a retrospective analysis of vinorelbine chemotherapy among patients with soft-tissue sarcomas at Memorial

Sloan-Kettering Cancer Center, one of seven patients with angiosarcoma had a partial response. No complete responses were seen in this study [85]. Another report from the same institution published a year earlier reported six patients with angiosarcoma treated with this agent where the median time to progression was 3 months [70].

Multiagent Chemotherapy

Doxorubicin/Ifosfamide

Combination chemotherapy with doxorubicin and ifosfamide tends to have durable responses among various treatment options that are currently available for angiosarcoma. Median progression-free survival for the combination of doxorubicin and ifosfamide in angiosarcoma is 5.4 months [70]. At our center, this approach is preferred for patients with noncutaneous angiosarcoma with a good performance status. For cutaneous angiosarcoma, patients are likely to have equivalent outcomes when compared with treatment with paclitaxel [78, 86]. Owing to the toxicity associated with treatment, it is preferable to use this combination early during the course of treatment of a patient with metastatic angiosarcoma when the hematopoietic reserve is good.

Gemcitabine/Docetaxel

Both gemcitabine and taxanes are effective agents against angiosarcoma, and the combination of gemcitabine and docetaxel has been reported to be effective in multiple case reports [87–89].

Targeted Therapies

Bevacizumab

The role of bevacizumab in angiosarcoma was evaluated in a phase II trial that enrolled 23 patients with angiosarcoma. Nine percent of them had a partial response, no complete responses were seen, 48 % had stable disease, and 43 % had progressive disease. Median progression-free survival was 12 weeks [19]. Combination of bevacizumab with cytotoxic chemotherapy such as paclitaxel is currently being investigated in a clinical trial.

Sunitinib

Several case reports [90, 91] have been published on the activity of sunitinib in angiosarcoma, but no large studies are available to determine response rates or the duration of response.

Sorafenib

In a phase II trial of sorafenib, 37 patients with angiosarcoma were enrolled. One complete response (3 %), four partial responses (11 %), and 21 patients (57 %) with stable disease were observed. Median progression-free survival was 3.2 months [92•]. Another phase II trial, by the French Sarcoma Group, enrolled 26 patients with superficial angiosarcoma and 15 patients with visceral angiosarcoma for treatment with sorafenib (800 mg daily). The overall response rate was 14.6 % at 4 months, which is identical to that in the earlier study. The response rate at 4 months was 15.4 % for superficial angiosarcomas and 13.3 % for visceral angiosarcomas. At 9 months, the nonprogression rate was 3.8 % for the superficial angiosarcomas and 0 % for the visceral angiosarcomas. In the 11 chemotherapy-naïve patients who received sorafenib, the response rate was 0 % [20•].

Pazopanib

Since its approval in 2012, pazopanib has been used in the treatment of angiosarcomas. Retrospective and prospective studies that look into the activity of pazopanib in angiosarcoma are currently lacking.

Prognosis

Median overall survival is 2.6 years [70], and the 5-year survival rate ranges from 31 % [70] to 35 % [93]. The location of the primary disease and the presence of metastasis are the key factors that affect survival [94]. When the disease is localized, median survival for the various sites is 3.6 years for head and neck angiosarcoma, 4.4 years for angiosarcoma of the extremities, 5.1 years for de novo breast angiosarcoma, 2.6 years for post-radiation-therapy breast angiosarcoma, and 2.1 years for angiosarcoma of the chest, abdomen, and pelvis [70]. Historically, the mean survival of patients developing angiosarcoma in the setting of a mastectomy has been reported to be significantly lower than that of patients with other angiosarcomas [95]. With the advent of more aggressive chemotherapy and radical surgery, the outcomes have certainly improved, but remain inferior to the survival for angiosarcoma in other locations. There is therefore considerable heterogeneity in biological behavior based on the location of the disease. The location can impact not only survival but also the response to specific chemotherapeutic agents, for instance, the efficacy of taxanes in the treatment of angiosarcoma is different for locations above and below the clavicle, thereby impacting prognosis [70].

Conclusions

Vascular sarcomas can range from indolent tumors such as EHEs to highly aggressive tumors such as angiosarcomas. EHEs can be observed until they start to grow relatively rapidly or produce significant symptoms. Clinical trials with a carefully selected patient population with progressive disease at a predetermined rate and a control arm are needed to understand the utility of various therapies in this slow-growing disease. Angiosarcomas, on the other hand, are aggressive and require multimodality care for optimal outcomes. Angiosarcomas tend to be multifocal, and systemic therapy in the neoadjuvant setting is strongly recommended for localized disease. Effective cytotoxic chemotherapies are available for metastatic angiosarcoma, but their durability is limited. Targeted therapies benefit a small proportion of patients, and identification of predictive markers for better patient selection is an important step in controlling these tumors.

Compliance with Ethics Guidelines

Conflict of Interest Vinod Ravi declares no conflict of interest. Shreyaskumar Patel declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer. 1982;50:970–81.
2. Mentzel T, Beham A, Calonje E, Katenkamp D, Fletcher CD. Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. Am J Surg Pathol. 1997;21:363–74.
3. Kleer CG, Unni KK, McLeod RA. Epithelioid hemangioendothelioma of bone. Am J Surg Pathol. 1996;20:1301–11.
4. Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer. 1999;85:562–82.
5. Mehrabi A, Kashfi A, Fonouni H, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer. 2006;107:2108–21.
6. Weiss SW, Goldblum JR. Hemangioendothelioma: vascular tumors of intermediate malignancy. In: Enzinger and Weiss's soft tissue tumors. 5th ed. Philadelphia: Mosby; 2008. p. 681–702.
7. Bhagavan BS, Dorfman HD, Murthy MS, Eggleston JC. Intravascular bronchiolo-alveolar tumor (IVBAT): A low-grade sclerosing epithelioid angiosarcoma of lung. Am J Surg Pathol. 1982;6:41–52.
8. Marino IR, Todo S, Tzakis AG, et al. Treatment of hepatic epithelioid hemangioendothelioma with liver transplantation. Cancer. 1988;62:2079–84.
9. Kelleher MB, Iwatsuki S, Sheahan DG. Epithelioid hemangioendothelioma of liver. Clinicopathological correlation of 10 cases treated by orthotopic liver transplantation. Am J Surg Pathol. 1989;13:999–1008.
10. Ben-Haim M, Roayaie S, Ye MQ, et al. Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? Liver Transpl Surg. 1999;5:526–31.
11. Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. Hepatogastroenterology. 1990;37:188–93.
12. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery. 1991;110:726–34. discussion 734-5.
13. Pichlmayr R, Weimann A, Ringe B. Indications for liver transplantation in hepatobiliary malignancy. Hepatology. 1994;20:33S–40S.
14. Madariaga JR, Marino IR, Karavias DD, et al. Long-term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. Ann Surg Oncol. 1995;2:483–7.
15. Furui S, Itai Y, Ohtomo K, et al. Hepatic epithelioid hemangioendothelioma: report of five cases. Radiology. 1989;171:63–8.
16. Holley MP, Cuschieri A. Epithelioid haemangioendothelioma of the liver: objective response to hepatic intra-arterial 5-FU. Eur J Surg Oncol. 1989;15:73–8.
17. Idilman R, Dokmeci A, Beyler AR, et al. Successful medical treatment of an epithelioid hemangioendothelioma of liver. Oncology. 1997;54:171–5.
18. Gambacorta M, Bonacina E. Epithelioid hemangioendothelioma: report of a case diagnosed by fine-needle aspiration. Diagn Cytopathol. 1989;5:207–10.
19. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013;24:257–63.
20. • Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). Cancer. 2013;119:2639–44. *Largest prospective clinical trial in EHE using a targeted therapy.*
21. Kayler LK, Merion RM, Arenas JD, et al. Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. Transplantation. 2002;74:128–30.
22. Mascarenhas RC, Sanghvi AN, Friedlander L, Geyer SJ, Beasley HS, Van Thiel DH. Thalidomide inhibits the growth and progression of hepatic epithelioid hemangioendothelioma. Oncology. 2004;67:471–5.
23. Sumrall A, Fredericks R, Berthold A, Shumaker G. Lenalidomide stops progression of multifocal epithelioid hemangioendothelioma including intracranial disease. J Neurooncol. 2010;97:275–7.
24. Otrock ZK, Al-Kutoubi A, Kattar MM, Zaatari G, Soweid A. Spontaneous complete regression of hepatic epithelioid haemangioendothelioma. Lancet Oncol. 2006;7:439–41.
25. Weiss SW, Goldblum JR. Malignant vascular tumors. In: Enzinger and Weiss's soft tissue tumors. 5th ed. Philadelphia: Mosby; 2008. p. 703–32.
26. Offori TW, Platt CC, Stephens M, Hopkinson GB. Angiosarcoma in congenital hereditary lymphoedema (Milroy's disease)—diagnostic beacons and a review of the literature. Clin Exp Dermatol. 1993;18:174–7.
27. Qureshi YA, Strauss DC, Thway K, Fisher C, Thomas JM. Angiosarcoma developing in a non-functioning arteriovenous fistula post-renal transplant. J Surg Oncol. 2010;101:520–3.

28. O'Connor JP, Quinn J, Wall D, Petrie JJ, Hardie JR, Woodruff PW. Cutaneous angiosarcoma following graft irradiation in a renal transplant patient. Clin Nephrol. 1986;25:54–5.
29. Conlon PJ, Daly T, Doyle G, Carmody M. Angiosarcoma at the site of a ligated arteriovenous fistula in a renal transplant recipient. Nephrol Dial Transplant. 1993;8:259–62.
30. Keane MM, Carney DN. Angiosarcoma arising from a defunctionalized arteriovenous fistula. J Urol. 1993;149:364–5.
31. Parrott NR, Scott PD, Freemont AJ, Johnson RW. Angiosarcoma in an arteriovenous fistula following successful renal transplantation—a case report. Transplantation. 1993;55:676–7.
32. Byers RJ, McMahon RF, Freemont AJ, Parrott NR, Newstead CS. Angiosarcoma at the site of a ligated arteriovenous fistula in a renal transplant recipient. Nephrol Dial Transplant. 1994;9:112.
33. Dargent JL, Vermylen P, Abramowicz D, et al. Disseminated angiosarcoma presenting as a hemophagocytic syndrome in a renal allograft recipient. Transpl Int. 1997;10:61–4.
34. Kibe Y, Kishimoto S, Katoh N, Yasuno H, Yasumura T, Oka T. Angiosarcoma of the scalp associated with renal transplantation. Br J Dermatol. 1997;136:752–6.
35. Bessis D, Sotto A, Roubert P, Chabrier PE, Mourad G, Guilhou JJ. Endothelin-secreting angiosarcoma occurring at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient. Br J Dermatol. 1998;138:361–3.
36. Wehrli BM, Janzen DL, Shokeir O, Masri BA, Byrne SK, O'Connell JX. Epithelioid angiosarcoma arising in a surgically constructed arteriovenous fistula: a rare complication of chronic immunosuppression in the setting of renal transplantation. Am J Surg Pathol. 1998;22:1154–9.
37. Ahmed I, Hamacher KL. Angiosarcoma in a chronically immunosuppressed renal transplant recipient: report of a case and review of the literature. Am J Dermatopathol. 2002;24:330–5.
38. Farag R, Schulak JA, Abdul-Karim FW, Wasman JK. Angiosarcoma arising in an arteriovenous fistula site in a renal transplant patient: a case report and literature review. Clin Nephrol. 2005;63:408–12.
39. Sanchez EQ, Marubashi S, Jung G, et al. De novo tumors after liver transplantation: a single-institution experience. Liver Transpl. 2002;8:285–91.
40. Johnson KH, Ghobrial HK, Buoen LC, Brand I, Brand KG. Nonfibroblastic origin of foreign body sarcomas implicated by histological and electron microscopic studies. Cancer Res. 1973;33:3139–54.
41. Hayman J, Huygens H. Angiosarcoma developing around a foreign body. J Clin Pathol. 1983;36:515–8.
42. Jennings TA, Peterson L, Axiotis CA, Friedlaender GE, Cooke RA, Rosai J. Angiosarcoma associated with foreign body material. A report of three cases. Cancer. 1988;62:2436–44.
43. Ben-Izhak O, Kerner H, Brenner B, Lichtig C. Angiosarcoma of the colon developing in a capsule of a foreign body. Report of a case with associated hemorrhagic diathesis. Am J Clin Pathol. 1992;97:416–20.
44. Ravi R. Primary angiosarcoma of the urinary bladder. Arch Esp Urol. 1993;46:351–3.
45. Schneider T, Renney J, Hayman J. Angiosarcoma occurring with chronic osteomyelitis and residual foreign material: case report of a late World War II wound complication. Aust N Z J Surg. 1997;67:576–8.
46. Ben-Izhak O, Vlodavsky E, Ofer A, Engel A, Nitecky S, Hoffman A. Epithelioid angiosarcoma associated with a Dacron vascular graft. Am J Surg Pathol. 1999;23:1418–22.
47. Cokelaere K, Vanvuchelen J, Michielsen P, Sciot R. Epithelioid angiosarcoma of the splenic capsule. Report of a case reiterating the concept of inert foreign body tumorigenesis. Virchows Arch. 2001;438:398–403.
48. Keymeulen K, Dillemans B. Epitheloid angiosarcoma of the splenic capsula as a result of foreign body tumorigenesis. A case report. Acta Chir Belg. 2004;104:217–20.
49. Mallick A, Jain S, Proctor A, Pandey R. Angiosarcoma around a revision total hip arthroplasty and review of literature. J Arthroplasty. 2009;24:323 e17–20.
50. Bach AD, Walgenbach KJ, Horch RE. Hemangiosarcoma of the left hand in a patient with the rare combination of Maffucci's and Stewart Treves syndrome. Vasa. 2000;29:71–3.
51. Davidson TI, Kissin MW, Bradish CF, Westbury G. Angiosarcoma arising in a patient with Maffucci syndrome. Eur J Surg Oncol. 1985;11:381–4.
52. Lennox EL, Draper GJ, Sanders BM. Retinoblastoma: a study of natural history and prognosis of 268 cases. Br Med J. 1975;3:731–4.
53. Dunkel IJ, Gerald WL, Rosenfield NS, Strong EW, Abramson DH, Ghavimi F. Outcome of patients with a history of bilateral retinoblastoma treated for a second malignancy: the Memorial Sloan-Kettering experience. Med Pediatr Oncol. 1998;30:59–62.
54. De Silva BD, Nawroz I, Doherty VR. Angiosarcoma of the head and neck associated with xeroderma pigmentosum variant. Br J Dermatol. 1999;141:166–7.
55. Leake J, Sheehan MP, Rampling D, Ramani P, Atherton DJ. Angiosarcoma complicating xeroderma pigmentosum. Histopathology. 1992;21:179–81.
56. Arora R, Sharma A, Gupta R, Vijayaraghavan M. Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. Indian J Pathol Microbiol. 2008;51:504–6.
57. Marcon I, Collini P, Casanova M, Meazza C, Ferrari A. Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. Pediatr Hematol Oncol. 2004;21:23–6.
58. Ploegmakers MJ, Pruszczynski M, De Rooy J, Kusters B, Veth RP. Angiosarcoma with malignant peripheral nerve sheath tumour developing in a patient with Klippel-Trenaunay-Weber syndrome. Sarcoma. 2005;9:137–40.
59. Millstein DI, Tang CK, Campbell Jr EW. Angiosarcoma developing in a patient with Neurofibromatosis (von Recklinghausen's disease). Cancer. 1981;47:950–4.
60. Riccardi VM, Wheeler TM, Pickard LR, King B. The pathophysiology of neurofibromatosis. II. Angiosarcoma as a complication. Cancer Genet Cytogenet. 1984;12:275–80.
61. Lederman SM, Martin EC, Laffey KT, Lefkowitch JH. Hepatic neurofibromatosis, malignant schwannoma, and angiosarcoma in von Recklinghausen's disease. Gastroenterology. 1987;92:234–9.
62. Brown RW, Tornos C, Evans HL. Angiosarcoma arising from malignant schwannoma in a patient with neurofibromatosis. Cancer. 1992;70:1141–4.
63. Png MA, Teh HS, Poh WT. Case report: angiosarcoma in a patient with von Recklinghausen's disease. Clin Radiol. 1996;51:521–3.
64. Sakaguchi N, Sano K, Ito M, Baba T, Fukuzawa M, Hotchi M. A case of von Recklinghausen's disease with bilateral pheochromocytoma-malignant peripheral nerve sheath tumors of the adrenal and gastrointestinal autonomic nerve tumors. Am J Surg Pathol. 1996;20:889–97.
65. Andreu V, Elizalde I, Mallafre C, et al. Plexiform neurofibromatosis and angiosarcoma of the liver in von Recklinghausen disease. Am J Gastroenterol. 1997;92:1229–30.
66. Elli M, Can B, Ceyhan M, et al. Intrathoracic malignant peripheral nerve sheath tumor with angiosarcoma in a child with NF1. Tumori. 2007;93:641–4.
67. Morphopoulos GD, Banerjee SS, Ali HH, et al. Malignant peripheral nerve sheath tumour with vascular differentiation: a report of four cases. Histopathology. 1996;28:401–10.
68. Mentzel T, Katenkamp D. Intraneural angiosarcoma and angiosarcoma arising in benign and malignant peripheral nerve sheath tumours: clinicopathological and immunohistochemical analysis of four cases. Histopathology. 1999;35:114–20.
69. McMenamin ME, Fletcher CD. Expanding the spectrum of malignant change in schwannomas: epithelioid malignant change, epithelioid

malignant peripheral nerve sheath tumor, and epithelioid angiosarcoma: a study of 17 cases. Am J Surg Pathol. 2001;25:13–25.
70. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005;11:241–7.
71. White CW, Wolf SJ, Korones DN, Sondheimer HM, Tosi MF, Yu A. Treatment of childhood angiomatous diseases with recombinant interferon alfa-2a. J Pediatr. 1991;118:59–66.
72. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. Ann Surg Oncol. 2013;20:1267–74.
73. Guadagnolo BA, Zagars GK, Araujo D, Ravi V, Shellenberger TD, Sturgis EM. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. Head Neck. 2011;33:661–7.
74. Candeias CM, Luis I, Ribeiro J, et al. Extended remission of metastatic epithelioid angiosarcoma of the heart with liposomal doxorubicin. BMJ Case Rep. 2010;2010.
75. Eiling S, Lischner S, Busch JO, Rothaupt D, Christophers E, Hauschild A. Complete remission of a radio-resistant cutaneous angiosarcoma of the scalp by systemic treatment with liposomal doxorubicin. Br J Dermatol. 2002;147:150–3.
76. Holloway CL, Turner AR, Dundas GS. Cutaneous angiosarcoma of the scalp: a case report of sustained complete response following liposomal Doxorubicin and radiation therapy. Sarcoma. 2005;9:29–31.
77. Wollina U, Fuller J, Graefe T, Kaatz M, Lopatta E. Angiosarcoma of the scalp: treatment with liposomal doxorubicin and radiotherapy. J Cancer Res Clin Oncol. 2001;127:396–9.
78. Italiano A, Cioffi A, Penel N, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer. 2012;118:3330–6.
79. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer. 2005;104:361–6.
80. Waldmann V. Liposomal doxorubicin in the treatment of metastasized angiosarcoma. Br J Dermatol. 2003;148:606.
81. Casper ES, Waltzman RJ, Schwartz GK, et al. Phase II trial of paclitaxel in patients with soft-tissue sarcoma. Cancer Invest. 1998;16:442–6.
82. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86:2034–7.
83. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008;26:5269–74.
84. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. Ann Oncol. 2012;23:501–8.
85. Anderson SE, Keohan ML, D'Adamo DR, Maki RG. A retrospective analysis of vinorelbine chemotherapy for patients with previously treated soft-tissue sarcomas. Sarcoma. 2006;2006:15947.
86. Penel N, Italiano A, Ray-Coquard I, et al. Metastatic angiosarcomas: doxorubicin-based regimens, weekly paclitaxel and metastasectomy significantly improve the outcome. Ann Oncol. 2012;23:517–23.
87. Arnaout A, Wedman DM, El-Sayed S, Acharya V, Lad S. Neoadjuvant gemcitabine-taxane chemotherapy for radiation-induced angiosarcoma of the breast: a case report. Breast J. 2012;18:276–8.
88. Shkoukani MA, Carron MA, Tulunay O, Kucuk O, Lin HS. Angiosarcoma of the scalp with complete response to a biweekly gemcitabine and docetaxel (GEMDOC) chemotherapy regimen. Ear Nose Throat J. 2011;90:E26–9.
89. Wilson R, Glaros S, Brown RK, Michael C, Reisman D. Complete radiographic response of primary pulmonary angiosarcomas following gemcitabine and taxotere. Lung Cancer. 2008;61:131–6.
90. Lu HJ, Chen PC, Yen CC, et al. Refractory cutaneous angiosarcoma successfully treated with sunitinib. Br J Dermatol. 2013. doi:10.1111/bjd.12258.
91. Yoo C, Kim JE, Yoon SK, et al. Angiosarcoma of the retroperitoneum: report on a patient treated with sunitinib. Sarcoma. 2009;2009:360875.
92. • Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27:3133–40. *Prospective clinical trial for targeted therapy in angiosarcoma using antiangiogenic agents*.
93. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer. 1996;77:2400–6.
94. Fayette J, Martin E, Piperno-Neumann S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol. 2007;18:2030–6.
95. Woodward AH, Ivins JC, Soule EH. Lymphangiosarcoma arising in chronic lymphedematous extremities. Cancer. 1972;30:562–72.