Chapter 13
Vascular Sarcomas

Vascular tumors run the gamut from benign hemangiomas to low-grade epithelioid hemangioendotheliomas, to highly aggressive angiosarcomas. We refrain in this section in discerning vascular sarcomas from similar tumors arising from lymphatics (lymphangiosarcomas) as there have not been good markers to definitively separate the two forms of tumors.

13.1 Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm with distinctive morphologic appearance, presenting as a deep painful soft tissue mass, although can be found primarily in lung, bone, and liver [1]. Multicentric presentation is often seen, particularly with visceral lesions (Fig. 13.1). The average age of presentation is 50 years, with no gender difference (Fig. 13.2).

The tumors are composed of epithelioid cells with densely eosinophilic cytoplasm, arranged in cords, strands, or nests and often with intracytoplasmic vacuoles (Fig. 13.3). Often there is a myxochondroid background and generally low mitotic rate. Mature vascular lumen formation is typically absent; this feature distinguishes EHE from other epithelioid vascular lesions, including epithelioid hemangioma and epithelioid angiosarcoma. Immunohistochemistry shows CD31, CD34, and ERG positivity [2]. The novel translocation t(1;3), resulting in *WWTR1-CAMTA1* fusion, has been identified in the majority of EHE samples examined [3, 4] and can be used as a very useful molecular test in challenging diagnosis. Additionally a small subset of EHE, with somewhat different morphologic appearance shows oncogenic activation of TFE3, as a result of *YAP1–TFE3* fusions [5]. This finding links EHE to other tumors with TFE3 oncogenic activation, such as alveolar soft part sarcoma and pediatric Xp11-renal cell carcinoma.

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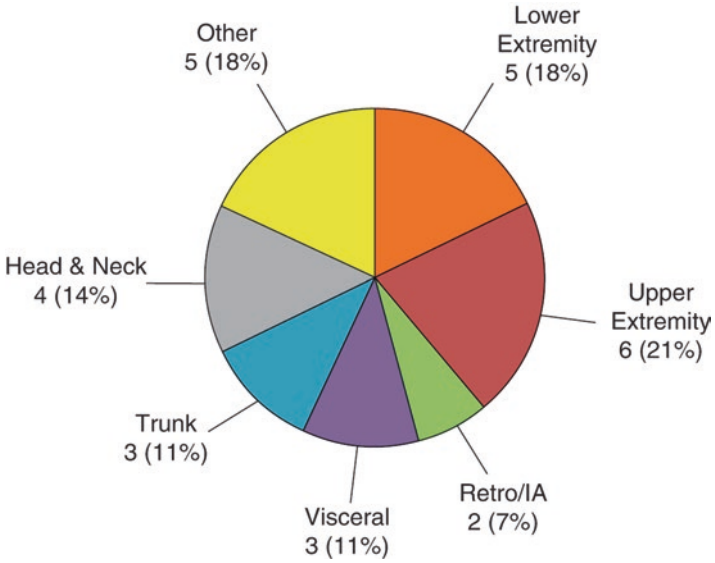

Fig. 13.1 Primary site distribution of adult patients with hemangioendothelioma. MSKCC 7/1/1982–6/30/2010 $n=28$. *Retro/IA* retroperitoneal/intra abdominal

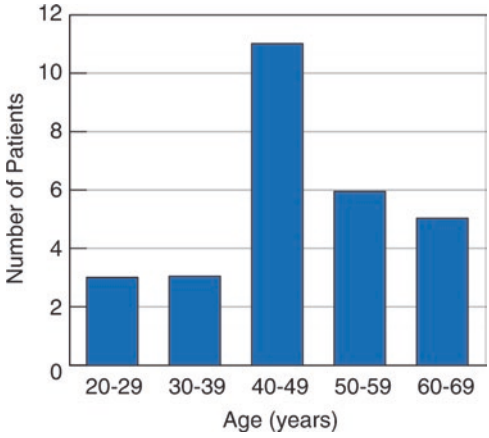

Fig. 13.2 Age distribution of adult patients with hemangioendothelioma. MSKCC 7/1/1982–6/30/2010 $n=28$

The tumor is most commonly seen as multifocal disease affecting liver, lung, pleura, or several of these sites simultaneously (Fig. 13.4). Various studies report 15 % local recurrence rates, 30 % with distal metastasis, and 50 % involvement with regional lymph nodes. Only a minority of these tumors progress over the course of 1–3 years with many appearing largely dominant for a decade or more suggesting observation as a viable option for management of such patients with unresectable multifocal disease. Approximately 20 % of EHE are more aggressive and thus may require immediate intervention.

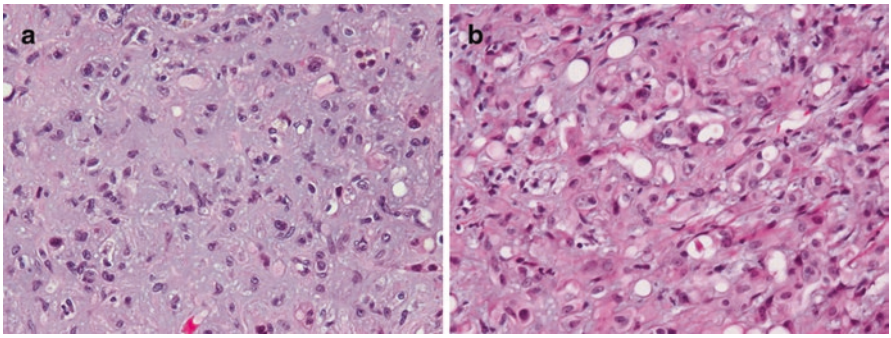

Fig. 13.3 (**a**) Microscopic appearance (H&E, ×200) of epithelioid hemangioendothelioma demonstrating bland, single epithelioid cells embedded in a distinctive myxochondroid stroma. (**b**) A second example demonstrating intracytoplasmic vacuoles with digested erythrocytes. In comparison to angiosarcoma, epithelioid hemangioendothelioma typically lacks the well-formed vascular channel formation and high degree of anaplasia

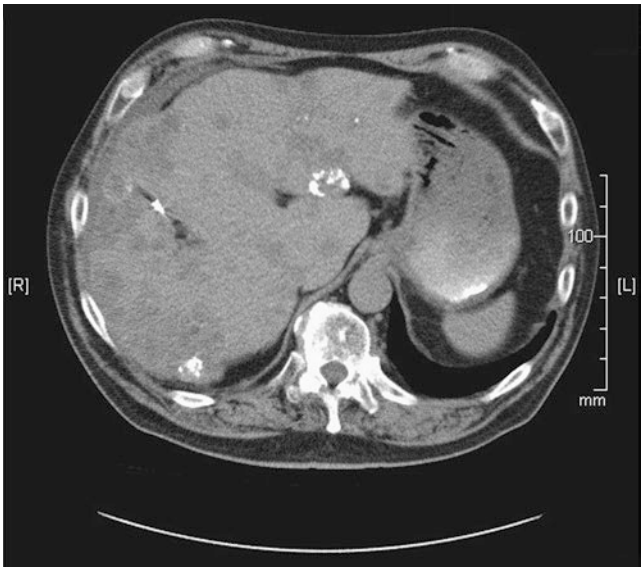

Fig. 13.4 Noncontrast CT image of multicentric epithelioid hemangioendothelioma affecting the liver. Heterotopic calcifications are demonstrated. The radiological abnormalities were essential unchanged over 5 years of monitoring

When feasible, primary treatment is surgical excision with an uncertain role for radiation and chemotherapy.

Liver-only disease has been treated with chemotherapy, bland embolization, chemo-embolization, or even liver transplant in those rare patients who develop liver failure from disease.

Table 13.1 Systemic therapy recommendations for epithelioid hemangioendothelioma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not used, given the low response rate of systemic therapy in metastatic disease
Metastatic disease	First line	A variety of agents have minor activity, but no consistent response pattern has been observed by the authors. Consideration can be given to liposomal doxorubicin/Doxil®/ Caelyx®, gemcitabine-based therapy, vinorelbine, and other agents. Hepatic embolization and other local therapies can be considered for liver-predominant disease. Doxorubicin + olaratumab is also approved in this situation but prospective data are lacking
	Second line	Pazopanib, or other oral VEGFR-blocking kinase inhibitor; clinical trials remain very relevant. Immune checkpoint inhibitors are not tested as of 2016 in epithelioid hemangioendothelioma

There has been only erratic responsiveness of EHE to chemotherapy; the authors have observed occasional responses to a number of chemotherapy agents but no reliable alternative as a definitive first-line agent or agents. There have been only hints of benefit in metastatic EHE patients from oral kinase inhibitors. In the largest prospective study including this diagnosis, 2/15 patients had a RECIST partial response to sorafenib; this study serves as a good baseline for evaluation of future therapeutics (Table 13.1) [6]. A high mitotic rate and marked nuclear atypia are independent predictors of survival [7]. The WHO classification suggests the use of 'malignant EHE' terminology for this group of lesions, to distinguish from the more bland appearing examples.

EHE should be distinguished from another fusion-positive vascular tumor, the so-called pseudomyogenic hemangioendothelioma (a.k.a. epithelioid sarcoma-like hemangioendothelioma). Most of these cases follow an indolent course, but occasionally behave aggressively and show distant spread; such as in this unusual example of a 30-year-old male (Fig. 13.5a–g) with metastatic disease to bone and soft tissue confined to the unilateral lower extremity—note the staining for vascular markers. Pseudomyogenic hemangioendotheliomas have characteristic t(7;19)(q22;q13) *SERPINE1-FOSB* translocations [8], different from the *ZFP36-FOSB* t(19;19) balanced translocations (or chromosomal 19 interstitial deletions) found in epithelioid hemangiomas [9].

13.2 Angiosarcoma/Lymphangiosarcoma

Angiosarcomas constitute a difficult family of tumors to manage, both given their local-regional failure as well as high risk of mortality from metastatic disease (Figs. 13.6 and 13.7). Angiosarcoma does present a unique profile of sensitivity to chemotherapy [10], and similar to leiomyosarcomas of different sites there appears to be differential sensitivity to systemic therapeutic agents based on the anatomic origin of the tumor (see earlier).

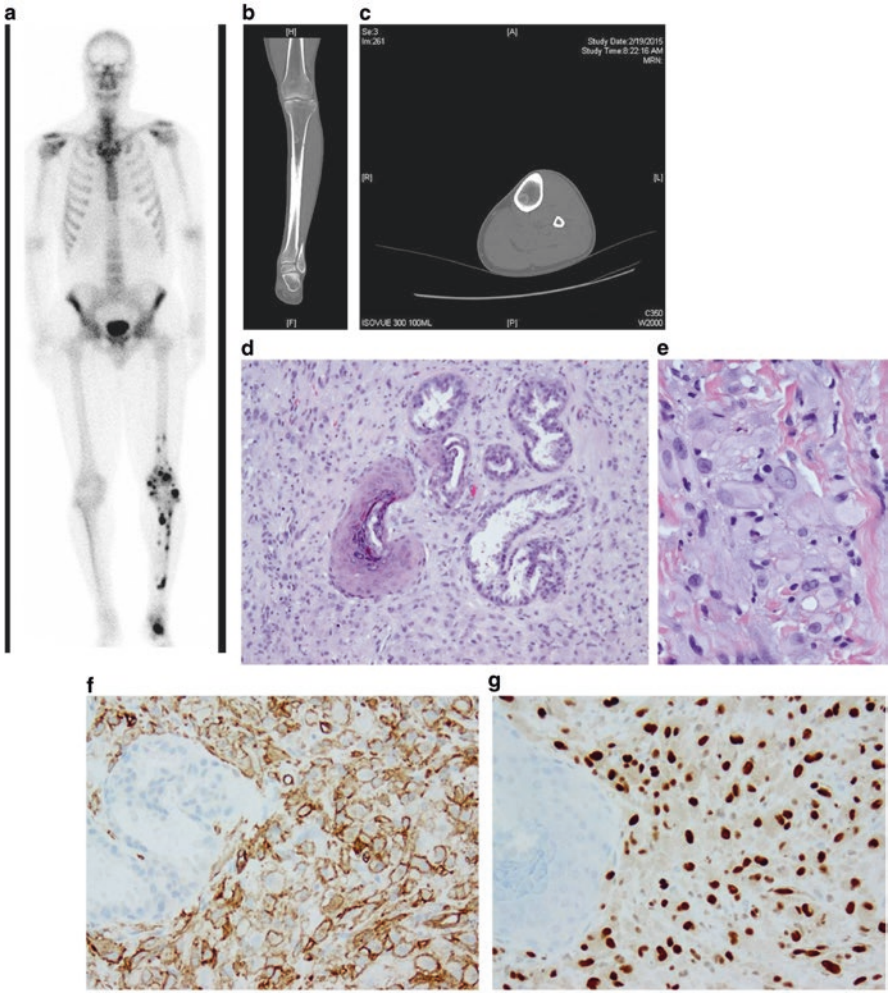

Fig. 13.5 (**a**–**c**) Case of pseudomyogenic hemangioendothelioma of the left lower leg—Has a positive bone scan, and good CT/MRI as variant of epithelial hemangioendothelioma. Bone scan and CT show multiple lesions within the distal femur and tibia. (**d**–**g**) Microscopic appearance showing tumor encasing skin adnexal structures, which at higher power have a distinctive epithelioid morphology with abundant, glassy eosinophilic cytoplasm. Tumor cells are diffusely positive for CD31 and ERG endothelial markers

Angiosarcomas tend to occur after age 50; the head and neck is a common primary site (Figs. 13.8, 13.9, and 13.10) [11–15]. Angiosarcomas have been observed in every conceivable location, and challenge surgeons and medical oncologists by their local regional recurrence risk and convincing but brief responses to a variety of systemic agents. Forms of angiosarcoma are associated with therapeutic radiation (Fig. 13.11) or lymphedema (Stewart–Treves syndrome) (Fig. 13.12), or lymphedema from other causes such as, filariasis [16] (Fig. 13.13) and are particularly

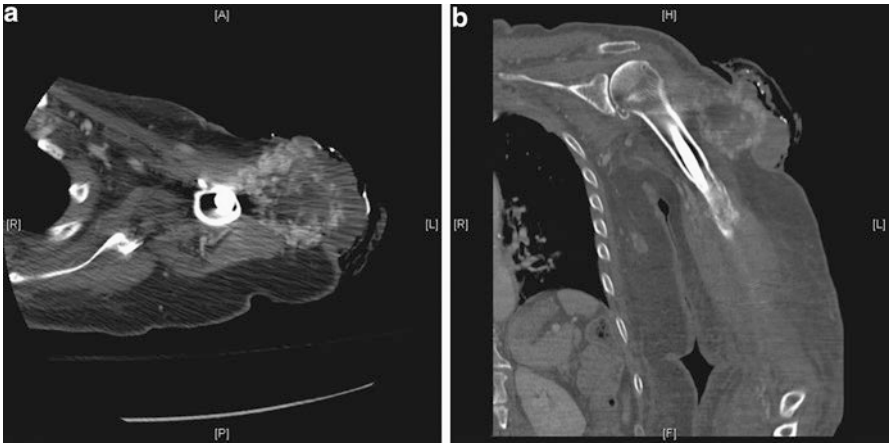

Fig. 13.6 CT images (**a**, **b**) of angiosarcoma of the humerus causing pathological fracture (s/p fixation) with demonstration of soft tissue metastases affecting the left upper extremity soft tissues

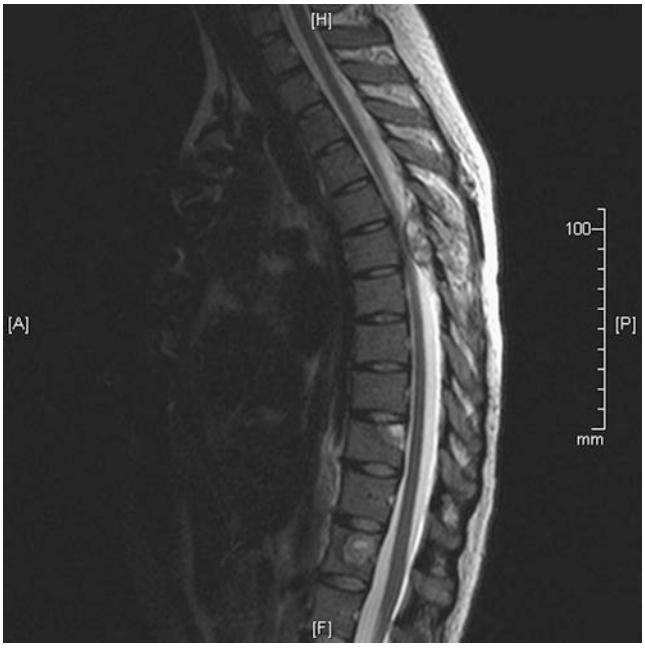

Fig. 13.7 T1 weighted MRI images of metastatic cardiac angiosarcoma with spinal metastases and invasion into the spinal canal

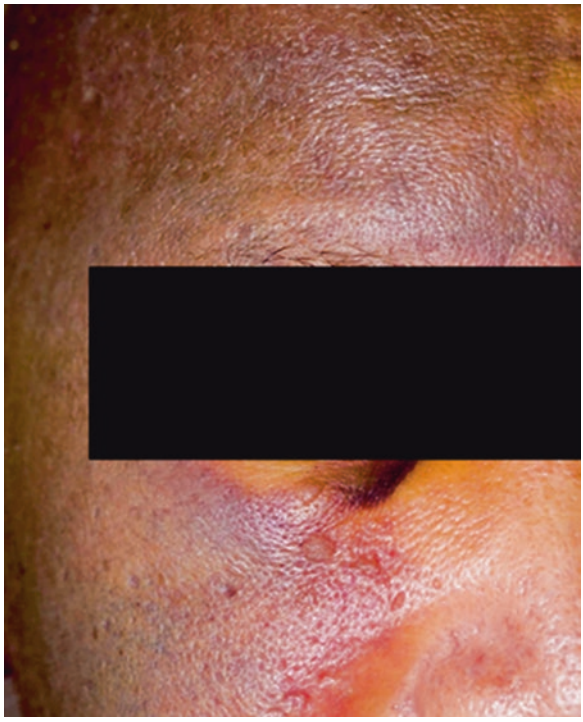

Fig. 13.8 Photograph of the upper right quadrant of the face in a 66-year-old Asian male demonstrating unresectable angiosarcoma involving the face, scalp, and neck

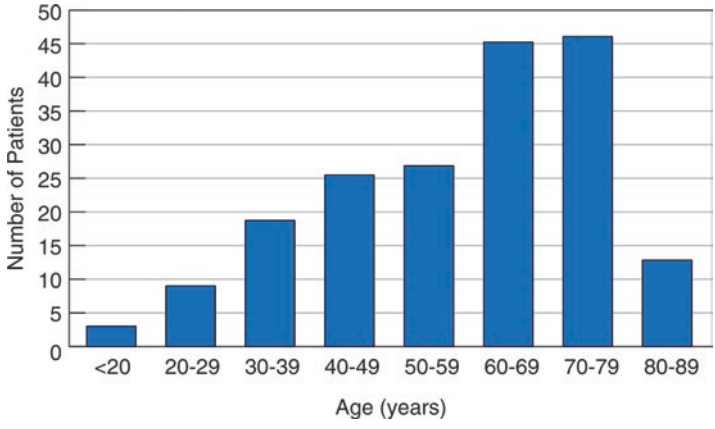

Fig. 13.9 Age distribution of adult patients with angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 188$

deadly in those settings, as are those that arise in bone as a primary site. Primary therapy, as for other sarcomas, includes excision with negative margins, and consideration of irradiation for those tumors that did not arise after prior radiation. In particular, in the head and neck area requires both wide margins and even larger radiation port if local-regional control is to be achieved.

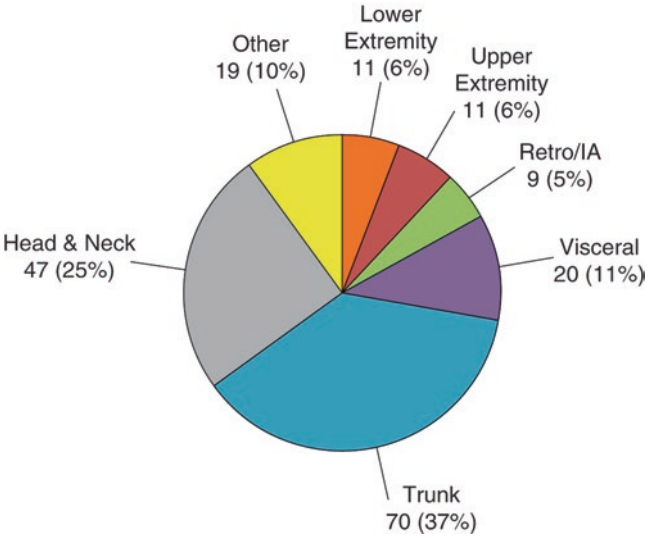

Fig. 13.10 Anatomic primary site distribution of adult patients with angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 187$. *Retro/IA* retroperitoneal/intra abdominal

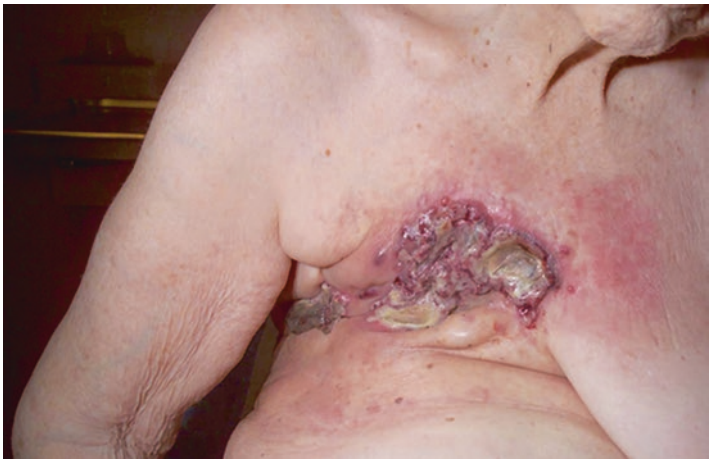

Fig. 13.11 Angiosarcoma of the right chest wall in a 77-year-old Caucasian woman 8 years after surgery and radiation therapy for infiltrating ductal adenocarcinoma of the breast

Tumors are typically CD31 and ERG positive, as expected for a cell of endothelial origin, and about half are positive for CD34. Microscopic imaging of a radiation-induced angiosarcoma is shown in Fig. 13.14. VEGFR3/FLT4 is positive by immunohistochemistry in a majority of cases, and positivity for KIT or cytokeratins are occasionally found in angiosarcomas as well. There is no characteristic genetic change in angiosarcomas known to date, although ~10 % of angiosarcomas (breast

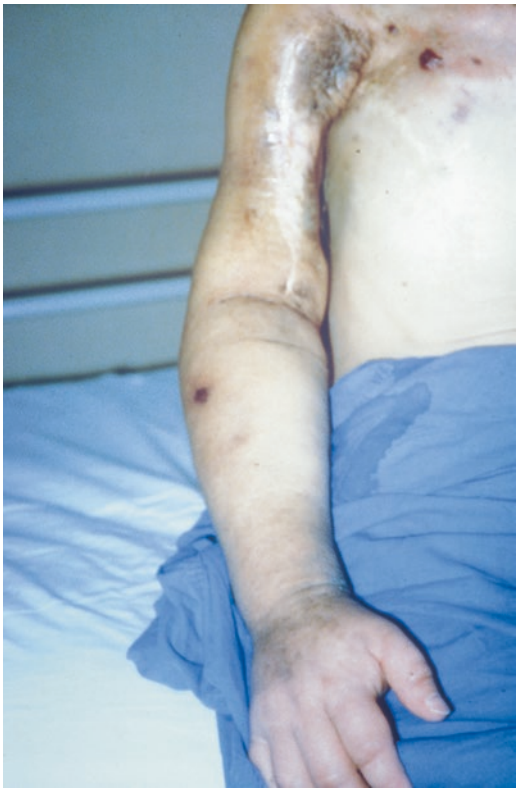

Fig. 13.12 Postmastectomy, postradiation lymphedema with multifocal lymphangiosarcoma (Stewart-Treves Syndrome) With permission from: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma*. London: Martin Dunitz Ltd., 1998

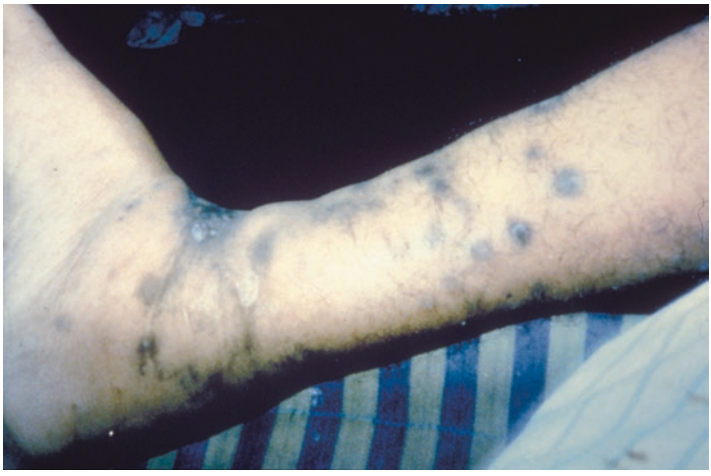

Fig. 13.13 Postfiliarial lymphedema with multifocal angiosarcoma. With permission from: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

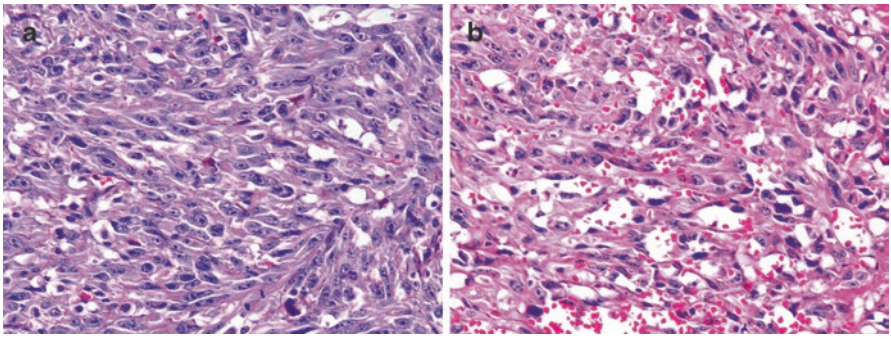

Fig. 13.14 Microscopic appearance (H&E, ×200) of postradiation angiosarcoma of the breast, demonstrating (**a**) a solid undifferentiated component with high mitotic activity and (**b**) a vasoformative component with inter-anastomosing, slit-like channels. The images are from the same primary tumor specimen

primaries or secondary to radiation for breast cancer) harbor mutations in *VEGFR2/KDR* [17]. It is not clear in that setting if the mutation is a driver or passenger mutation, but the overexpressed gene can be inhibited with VEGFR inhibitors such as sunitinib or sorafenib. Using multiple sequencing technologies on 39 angiosarcomas, mutations in *PTPRB* and *PLCG1* were found in 26 % and 9 % of samples [18]. PTPRB will prove hard to target, since it is a phosphatase, and replacing its activity after truncating mutations is tantamount to replacing a tumor suppressor gene. Another sequencing study underscored that mutation of elements of the MAPK pathway are mutated in over half of angiosarcomas, including mutations or amplifications in over half of the angiosarcomas ($n = 18$, 53 %) harbored genetic alterations affecting the MAPK pathway, involving mutations in *KRAS, HRAS, NRAS, BRAF, MAPK1*, and *NF1*, or amplifications in *MAPK1/CRKL, CRAF,* or *BRAF* [19].

Given a tumor that is chemotherapy sensitive but frequently progressing after a relatively short interval, adjuvant chemotherapy can be considered with active agents such as anthracyclines and taxanes [10, 20, 21]. However, it is not clear if adjuvant chemotherapy impacts survival in this disease. Ifosfamide has somewhat less active in angiosarcoma than in other sarcoma subtypes, in our experience.

Angiosarcomas appear to respond as well as other sarcomas to first-line chemotherapy. In a pooled analysis of 108 locally advanced and metastatic angiosarcoma patients separated from 2557 patients with other STS histologies, 25 % of angiosarcoma patients had a measured CR or PR to therapy. The median PFS was 4.9 months and OS 9.9 months [22].

Agents such as bevacizumab, sorafenib, and sunitinib directed against VEGF receptors have some activity against angiosarcomas. We have observed the best responses in women with breast angiosarcomas, while for other sites such as head and neck we have observed (at best) stable disease to blanching of extensive tumor lesions, but few if any overt partial responses (Table 13.2) [23]. However, a study from France demonstrated little activity of sorafenib in angiosarcoma patients [24]. While the RECIST response rate was 15 % in the patients with superficial tumors,

Table 13.2 Systemic therapy recommendations for angiosarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		To consider any or all of anthracycline, taxane, or ifosfamide; may at least delay recurrence; some investigators use paclitaxel and radiation followed by surgery for resectable or marginally resectable primary tumors
Metastatic disease	First line	Anthracycline + olaratumab or taxane if not given; gemcitabine or combination. Paclitaxel is as effective as paclitaxel and bevacizumab, thus combination therapy with the two is not indicated
	Second line	Pazopanib, single agent bevacizumab, or other oral VEGFR-blocking kinase inhibitor; ifosfamide; clinical trials remain very relevant. There are anecdotal data as of 2016 that angiosarcomas can be sensitive to PD1 inhibitors or combinations with other immune checkpoint inhibitors

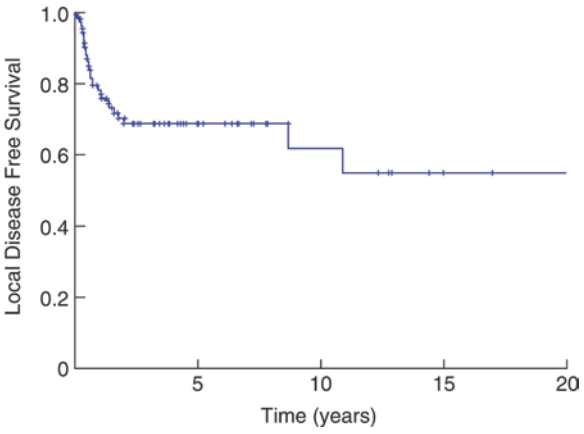

Fig. 13.15 Local disease-free survival for adult patients with primary angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 108$

the median PFS was under 2 months in this cohort. Furthermore, there is no synergy between paclitaxel and bevacizumab; patients receiving the combination fared no better than those receiving single agent paclitaxel [25].

The Dabska tumor is a low-grade angiosarcoma often appearing in the skin particularly that of children. It has a characteristic histological appearance with vascular channels and papillary pouching. The lesion is very rare and was originally described by Maria Dabska in 1969 [26].

13.3 Outcome

Local disease-free survival is shown in Fig. 13.15, for those with primary presentation and disease-specific survival in Fig. 13.16, emphasizing the high risk of metastatic disease even in those with only a primary tumor at presentation.

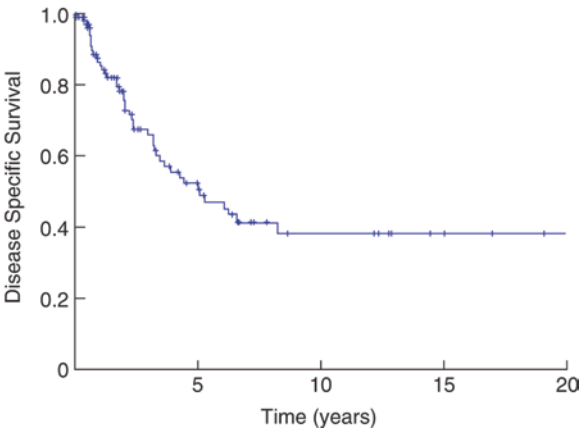

Fig. 13.16 Disease-specific survival for adult patients with primary angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 108$

13.4 Kaposi Sarcoma

Kaposi sarcoma (KS) has "historically" been a complicating factor of HIV (human immunodeficiency virus) disease, although Kaposi first described it in 1872 [27, 28]. It is less well appreciated that it also arises endemically in a population with low CD4+ T cell counts in the Mediterranean basin and in Africa, where it is most commonly observed. A version of KS has been recognized more recently in people who are therapeutically immunosuppressed to prevent rejection of organ transplants. In each situation, human herpesvirus-8 (HHV8, also called Kaposi sarcoma herpesvirus, KSHV) is the etiological agent. What was once a devastating disease in the HIV population has been largely suppressed with the use of ART (antiretroviral therapy), such that cases of KS are now relatively uncommon in the HIV population. It is not clear if there are direct effects of HIV-directed therapy against HHV8, or if improvement in CD4+ T cell counts is most responsible for the improvement in such patients. In endemic cases and in HIV-related cases alike, local therapy can be active for skin lesions and systemic therapy can be used for visceral disease or when local therapies fail.

KS affects skin most commonly, but also involves lymph nodes and visceral organs, in particular the gastrointestinal tract. Since KS typically affects multiple sites of skin, surgery is usually not indicated. Local control of individual skin lesions can be achieved by a number of means, be it alitretinoin gel, which was proved effective in controlling the plaque form of the disease [29] compared with a placebo gel alone, and other agents with anti-KS activity include intralesional vinca alkaloids [30], intralesional sodium tetradecyl sulfate (a soap) [30], and other topical agents.

The viral pathogenesis of KSHV/HHV8 is revealing important aspects of angiogenesis. The viral G protein coupled receptor vGPCR/ORF74 is a critical component of the virus in pathogenesis [31]. Proinflammatory pathways such as EphrinA2

Table 13.3 Systemic therapy recommendations for Kaposi sarcoma

Clinical scenario		Comments
Primary therapy	First line	Depends on anatomic distribution; can involve topical or intralesional therapy for skin-only disease; taxanes or PLD is a good option for systemic therapy for disseminated disease. Doxorubicin + olaratumab is technically approved in this situation, but prospective data are lacking
Persistent/metastatic disease	First line	Agent not used earlier; lenalidomide has activity, as may oral etoposide; TOR inhibitors such as sirolimus in patients not on antiretroviral therapy (pharmacodynamic interaction)
	Second line	Clinical trials, including those involving immune checkpoint inhibitors; VEGFR targeted tyrosine kinase inhibitors—caution should be taken regarding interaction with anti-HIV medications (thus coordinated care with HIV physician is a must)

*PLD: pegylated liposomal doxorubicin; VEGFR: vascular endothelial growth factor receptor

serve as a receptor for the virus, usurping a guidance mechanisms used by neurons and blood vessels for propagation by triggering endocytosis of the virus [32]. Interestingly, EphrinB2, another angiogenesis related gene, is upregulated by epigenetic modifier EZH2, suggesting another pathway that is usurped by KSHV for survival [33]. Finally, paradoxically, the mTOR pathway is involved in KSHV signaling and the immunosuppressive TOR inhibitors such as sirolimus could inhibit critical viral functions [34]. As a result, a number of options exist for new therapies for treatment of Kaposi sarcoma that were not considered even a few years ago.

In terms of randomized studies involving actively used agents, pegylated liposomal doxorubicin (PLD, Caelyx®/Doxil®) has been shown superior to combination chemotherapy in at least two randomized studies and is a good standard of care for local disease refractory to other therapy, or for disseminated disease [35, 36], though paclitaxel appeared to have superior progression-free survival in one randomized study [37]. PLD is less toxic than liposomal daunorubicin, which was also shown useful in KS [38]. Taxanes are active against KS [37, 39], as are a variety of agents tested in phase II studies such as interferon-alfa [40], interleukin-12 [41], or etoposide [42]. Since the first publication of disappearance of KS lesions in solid tumor organ transplant patients after switching immunosuppression from cyclosporine to sirolimus [43], other case reports have supported the utility of mTOR inhibitors in Kaposi sarcoma. The use of sirolimus in the HIV+ KS population has been limited by pharmacodynamic interaction between protease inhibitors and sirolimus [44]. (Table 13.3) There are case reports that lenalidomide is active in patients with Kaposi sarcoma, the subject of an ongoing clinical trial [45]. In principle, oral VEGFR kinase inhibitors could inhibit KSHV signaling, but again, pharmacodynamic interactions often interfere with use of these agents for people on commonly used antiretroviral agents, which affect cytochrome P450 3A4 metabolized compounds. Bevacizumab has at least some activity and does not interfere with the cytochrome P450 system [46].

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