Cutaneous Sarcomas

Brittny N. Tillman, MD[a,*], Jeffrey C. Liu, MD[b]

KEYWORDS

- Sarcoma • Cutaneous • Surgery for cutaneous sarcoma
- Dermatofibrosarcoma protuberans • Atypical fibroxanthoma
- Pleomorphic dermal sarcoma • Leiomyosarcoma • Angiosarcoma

KEY POINTS

- The various types of cutaneous sarcomas are discussed including presentation, diagnosis, and management.
- Adequate biopsy and a thorough pathologic analysis are critical to diagnosis.
- The mainstay of treatment is surgical resection with complete margin analysis given propensity for recurrence.

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a low-grade cutaneous sarcoma with an approximate yearly incidence of 4 cases per million in the United States (**Tables 1** and **2**).[1] It is among the most common of cutaneous sarcomas, accounting for 18% of the overall incidence with peaks in the third to fifth decades of life.[2] There is also an increased incidence in black patients and women.[3]

DFSP originates from dermal fibroblasts and possibly dermal dendrocytes. It is associated with a t(17;22) (q22:q13) translocation that results in the fusion of a beta-type platelet-derived growth factor receptor gene to the COL1A1 (collagen type 1 alpha 1) gene. Excessive activation of the beta-type platelet-derived growth factor receptor–dependent signaling pathway results in uncontrolled cell growth.[4]

DFSP usually presents as a slow growing asymptomatic plaque most commonly on the trunk followed by lower extremities and scalp. Untreated, DFSP can become very large, locally invasive, and destructive.[2] DFSP has a high reported recurrence rate of 50%; when excised with margins that are greater than 2 cm, the recurrence rate improves to 13%.[5] Although positive margins are more frequent with wide local excision than Mohs micrographic surgery (MMS), the local recurrence rates have been

[a] Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical School, 2001 Inwood Road, Dallas, TX 75390-8868, USA; [b] Department of Otolaryngology–Head and Neck Surgery, Lewis Katz School of Medicine at Temple University, Fox Chase Cancer Center, 3440 North Broad Street, Philadelphia, PA 19140, USA
* Corresponding author.
E-mail address: brittny.tillman@utsw.edu

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Table 1
Characteristics of patient population and presentation by tumor type

Tumor	Population	Presentation
DFSP	Peak in third to fifth decades More common in women More common in black patients	Slow growing plaque with one or more nodules Erythematous, brown, or skin colored Often >3 cm at presentation
Atypical fibroxanthoma	Peak in seventh to eighth decades More common in men	Rapid growth of firm, nodular, exophytic tumor on sun damaged skin Erythematous or skin colored May become ulcerated
Pleomorphic dermal sarcoma	Peak in eighth decade More common in men	Rapid growth of exophytic, nodular, or plaque like tumor on sun damaged skin Brown or erythematous
Cutaneous leiomyosarcoma	Peak in sixth decade More common in men More common in white patients	Nodules or plaques which may be irregular or ulcerative Skin colored May be associated with pain, itching, and/or bleeding
Angiosarcoma	Average seventh Decade May present 2–30 y after radiation May present 10–15 y after lymphedema	Highly variable Red cutaneous lesion similar to hematoma May also seem to be similar to rosacea, eczema, plaque, nodule, cellulitis, or cutaneous edema

statistically similar.[6] One series of 204 retrospective patients with DFSP showed a recurrence rate of 1% using wide excision as a standardized approach, emphasizing the importance of margin control.[7]

The overall prognosis of DFSP is excellent with a 10-year survival rate of 99.1%.[1] Classic DFSP has a rare metastasis rate of 1% to 4%, with the lungs being the most common site.[5] Negative prognostic factors include advanced patient age at the time of diagnosis, large tumor size, and male sex.[8] Histologic variants include Bednar, myxoid, giant cell fibroblastoma, sclerosing, atrophic, and fibrosarcomatous. The fibrosarcomatous variant exhibits the highest rate of metastasis (14%) and poorest prognosis.[2,9,10]

On pathologic analysis, DFSP is characterized by storiform, monomorphic spindle cells, and minimal atypia. The infiltration of adipose tissue by tumor is characterized by a honeycomb appearance. Tumors stain positively for CD34 and negatively for factor XIIIa with rare exceptions. CD34 is an important immunohistochemical marker that may be absent in less differentiated cases. In these cases reverse transcriptase polymerase chain reaction or fluorescence in situ hybridization may be diagnostically useful in identifying the characteristic t(17;22) (q22;q13) translocation.[2]

MRI should be considered if extracutaneous extension is suspected.[11] In advanced tumors and more aggressive subtypes such as fibrosarcomatous, a metastatic workup including lung imaging with a chest computed tomography scan should also be considered.[2,12]

Table 2
Pathogenesis, histologic findings, and treatment strategy by tumor type

Tumor	Pathogenesis	Histology	Treatment
DFSP	Dermal fibroblasts and dendrocytes t (17;22) (q22:q13) translocation	Monomorphic spindle cells with minimal atypia (+) CD34 and (−) factor XIIIa	Wide excision with 2–4 cm margins vs Mohs MRI for extensive disease Regional/distant imaging for fibrosarcomatous subtype Radiation therapy vs imatinib for select cases
Atypical fibroxanthoma	Myofibroblastic cells P53 and telomerase reverse transcriptase mutations	Dermal atypical spindle, pleomorphic, histiocytic, and multinucleated giant cells with occasional atypical mitosis Diagnosis of exclusion	Wide excision with at least 1–2 cm margins vs Mohs Consider imaging for advanced disease[a]
Pleomorphic dermal sarcoma	Possibly a deeper and more aggressive variant of AFX P53, HRAS, CDKN2A, PIK3CA mutations	Resembles AFX with a predilection for subcutaneous structure invasion, perineural invasion, and necrosis Diagnosis of exclusion	Wide excision with at least 1–2 cm margins vs Mohs Consider imaging given 10% risk of metastasis[a]
Cutaneous leiomyosarcoma	Erector pili muscles of hair follicles	Interlacing fascicles of spindle cells with mitotic figures (+) Vimentin and smooth muscle actin (+) Desmin, cytokeratin, S100 in some cases	Wide excision with 3–5 cm margins vs Mohs Consider imaging for advanced disease[a] Adjuvant radiation therapy for tumors >5 cm Multiple systemic regimens reported for advanced disease
Angiosarcoma	Vascular endothelial cells	Dilated disorganized vascular structures or high-grade epithelioid spindle cells without clear vessels High mitotic rates	Preoperative mapping biopsies Wide excision with at least 3 cm margins Consider imaging for advanced disease[a] Multiple systemic regimens reported for advanced and metastatic disease Poor prognosis

[a] No formal guidelines exist.

Once the diagnosis is confirmed, the treatment of choice includes both wide local excision with generous margins of 2 to 4 cm and MMS. Given its widely infiltrative nature, excision should extend to investing fascia of muscle or pericranium when feasible. Margin control may require hematoxylin and eosin sections supplemented by CD34 immunohistochemistory.[13] When MMS is used, a debulking specimen should be examined to identify the more aggressive fibrosarcomatous transformation.[11]

Any complex closure should be delayed until after the final margins are cleared histologically.[2,14] Elective nodal dissection is not advised secondary to infrequent regional nodal metastasis (1%).[5] Although DFSP is radiosensitive, radiation therapy is usually used in either adjuvant or palliative contexts.[2]

Imatinib is a proven systemic therapy to be considered for unresectable, recurrent or metastatic DFSP. It is a multikinase inhibitor in the PDGFRB signaling pathway dysregulated by the t(17;22) translocation often seen in DFSP.[15] It is important to note that tumors lacking the t(17;22) translocation may not respond to imatinib and therefore molecular analysis is recommended before the initiation of imatinib therapy.[13]

ATYPICAL FIBROXANTHOMA

Atypical fibroxanthoma (AFX) is a low-grade superficial sarcoma often considered a superficial variant of dermal pleomorphic sarcoma. The true overall prevalence of AFX is difficult to elucidate because it is a diagnosis of exclusion, which is fraught with misclassification. It is seen more often in the seventh and eighth decades of life and is more common in men.[2]

UV light is thought to contribute to malignant transformation of myofibroblastic cells leading to AFX. Additional studies show telomerase reverse transcriptase promotor mutations and dysregulation of the CCND1/CDK4/6/RB1 signaling pathway, allowing cells to escape apoptosis through telomerase activation as well as decouple the cell cycle with subsequent tumor cell proliferation.[16,17]

AFX typically arises in the head and neck of elderly patients and less commonly in sun-exposed extremities.[18] It typically presents as an exophytic tumor on sun-damaged skin with a tendency toward rapid growth (over weeks).[2] They may become large and ulcerated.[17] Histologically, AFX is predominantly confined to the dermis with atypical spindle or pleomorphic cells, histiocytic cells, and multinucleated giant cells in variable growth patterns with occasional atypical mitosis. There may be hemorrhagic areas and ample vasculature. It is a well-circumscribed pleomorphic neoplasm with increased proliferation, lacking tumor necrosis and infiltrative growth.[18]

Ultimately, AFX is a diagnosis of exclusion and should include a panel of immunostains to rule out other tumor types.[18] It is critical that amelanotic melanoma be ruled out with appropriate markers such as S100 and pancytokeratin.[17] Although vimentin and CD68 staining may be positive, there is no immunohistochemical marker that allows for unequivocal diagnosis.

AFX is thought to represent a less aggressive and superficial version of pleomorphic dermal sarcoma (PDS), the cutaneous variant of undifferentiated pleomorphic sarcoma. Prior research has failed to make the distinction between AFX and dedifferentiated sarcomas, leading clinicians to question the true metastatic potential of AFX.[17] There is ongoing debate on a definitive distinction between AFX and PDS.[19]

The initial workup should include a history and physical examination, complete skin and regional nodal examination, and biopsy. Punch, incisional, or core biopsies are preferred to decrease misdiagnosis associated with a superficial specimen. The role of clinical imaging is unclear, but regional nodal evaluation can be considered with

an ultrasound examination or a computed tomography scan, particularly for advanced cases.[17]

Treatment of the primary includes wide local excision with at least 1- to 2-cm margins or MMS. The entire specimen should be evaluated for infiltration beyond the dermis.[17] Regional nodal dissection should be performed as clinically indicated, although there are no absolute guidelines for management. Although metastasis has been reported in 0.5% to 10.0% of all cases, in general, metastasis is rare and the prognosis is generally favorable.[17]

PLEOMORPHIC DERMAL SARCOMA

PDS is also referred to as cutaneous pleomorphic sarcoma and cutaneous undifferentiated pleomorphic sarcoma, which has led to confusion with regard to its true incidence. Furthermore, it is thought to be both a superficial variant of soft tissue undifferentiated pleomorphic sarcoma and a deep variant of AFX. It has also fallen under the term "malignant fibrous histiocytoma," which was previously used to classify most dedifferentiated sarcomas and is no longer used.[17] Because CUPS is a fairly new entity, there are currently no reliable reporting of overall incidence rates. It is diagnosed most often in the eighth decade of life and is more common in men.[2]

PDS typically presents as an exophytic, nodular, or plaque-like growth on sun-damaged skin with rapid growth in elderly patients.[2] PDS resembles a more aggressive form of AFX, although the histopathologic distinction between the 2 entities is not clearly defined. PDS has a predilection for subcutaneous structure invasion, perineural invasion, and necrosis.[17,20]

Like AFX, PDS is also a diagnosis of exclusion that should evaluated with an adequate biopsy and immuhistochemistry.[18] Amelanotic melanoma must be ruled out.[17] Regional metastasis has been described in up to 10% of cases; therefore, radiologic nodal evaluation should be considered.[17] The treatment of choice is excision with at least 1- to 2-cm margins.[19]

CUTANEOUS LEIOMYOSARCOMA

Cutaneous leiomyosarcoma (LMS) is a rare cutaneous sarcoma that presents later in life, with an average age of diagnosis at 62 years. It presents predominantly in white males (94% white and 78% male).[21] Cutaneous LMS is separated into 2 main groups: a cutaneous (dermal) malignancy that rarely metastases, and a subcutaneous variant with greater metastatic potential. LMS can also arise from visceral sites, like the uterus or retroperitoneum, with metastasis to other sites. This review focuses on the cutaneous types.

The presentation of LMS is evenly distributed across the body: 25.5% in the lower limb and hip, 24.0% in the upper limb and shoulder, and 22.5% in the trunk 27.9%, as reported in the Surveillance, Epidemiology, and End Results database.[21] The cutaneous LMS subtype presents more frequently in the head and neck, representing 48% of cutaneous LMS cases.[22,23] Cutaneous LMS is thought to arise from the erector pili muscles of the hair follicles, whereas subcutaneous LMS is thought to arise from smooth muscle in vessels, although this remains speculative. LMS lesions present as skin-colored or erythematous nodules or plaques. They can be irregular or ulcerative. Pain is sometimes associated with presentation, although itching, burning, and bleeding can also occur.[24] Most of these findings described are usually seen with cutaneous LMS, with subcutaneous LMS presenting with normal overlying skin.

Histologically, LMS shows interlacing fascicles of spindle cells, usually with mitotic figures. For cutaneous LMS, these are vimentin and smooth muscle actin positive.

Desmin is positive in approximately 60% of cases.[25] Cytokeratins and S100 stains may occasionally be positive.[26] Necrosis, sclerosis, hemorrhage, hyalinization, and myxoid changes may occasionally be seen.[27]

Cutaneous LMS have a different metastatic pattern compared with subcutaneous LMS, although the data are limited. Although metastasis with cutaneous LMS has been rarely reported, as many as 30% of metastasis were reported in subcutaneous LMS.[24] After an appropriate workup, for disease confined to the local site the mainstay of treatment is surgical resection. Like all sarcomas, negative histologic margins are important to achieve. Some studies have recommended a 3- to 5-cm margin, which is very difficult to achieve in the head and neck.[23] Adjuvant therapy with radiation therapy is generally recommended for lesions greater than 5 cm in size, as noted in the National Comprehensive Care Network guidelines.[13,28] MMS has been reported for LMS with good results and acceptable local control rates.[29]

Despite appropriate treatment, recurrence remains an issue. For cutaneous LMS, the recurrence rate is lower, with 1 series reporting a rate as low as 14%. For subcutaneous LMS, the recurrence rate is reported to be much higher, with as many as one-half of all patients having a recurrence.[23,27] Distant metastases with the subcutaneous variant are uncommon and present in approximately 15% of cases, most commonly to the lungs.[27] For advanced disease, multiple chemotherapy regimens have been reported, which include the use of doxorubicin, ifosfamide, dacarbazine, and gemcitabine.[27] Additional treatment with tyrosine kinase inhibitors in LMS have been reported in clinical trials on sarcoma.[30]

ANGIOSARCOMA

Angiosarcomas (AS) are rare tumors that arise from vascular endothelial cells. They are aggressive tumors, with difficult rates of local control and a high rate of metastasis. The most common type is spontaneous formation in the head neck, known as the Wilson–Jones type. The tumor is rare, and represents about 10% of head and neck sarcomas.[31] AS can also present as a radiation-induced cancer, or develop after chronic lymphedema.[32,33] For the purpose of this review, we focus on cutaneous AS that present spontaneously in the head and neck.

The presentation of AS is varied and its diagnosis is difficult. It can present as a red lesion like a cutaneous hematoma, but may also have a similar presentation to rosacea, eczema, plaque, nodule, cellulitis, or cutaneous edema.[34] Histologically, the AS is variable as well. The cancer can have dilated disorganized vascular structures, with similarities to a hemangioma, but may also present as high-grade epithelioid spindle cells without clear vessels. The malignant endothelium may appear pleomorphic with varied growth patterns. Mitotic rates are usually very high.[35] The presence of an epithelioid morphology and necrosis are both associated with a worse prognosis.[36] For head and neck AS, the most common presentation site is the scalp and neck (61%) and the face (34%).[37]

In evaluating the patient with AS, a workup for both local and regional disease is recommended. MRI may be a consideration for these lesions given the soft tissue nature of the disease. A Surveillance, Epidemiology, and End Results database analysis showed that although 51% of patients were reported as having only localized disease, an additional 23% presented with regional disease, supporting the need for regional evaluation.[38] Distant metastasis was rare (8%).

Surgery remains the mainstay of therapy for treatment, with adjuvant radiation common.[37] A significant challenge in this disease is difficulty in achieving negative histologic margins on the primary site. Only about 20% to 47% of AS resection margins

are reported as histologically negative.[38] Recurrence rates of 63% have been reported.[39] Unfortunately, the outcomes of patients who undergo resection with residual positive margins are almost no different than patients who do not receive surgery at all.[37] Neoadjuvant chemotherapy has been advocated as a treatment concept and is under investigation.[40,41]

To help better establish the margin of resection, preoperative localization and mapping biopsies have been advocated. Biopsies at the planned resection margin are taken preoperatively, usually with a punch biopsy, to map out the resection. The recommended margin size varies, but margins of 3 cm or more have been advocated.[13] A distinct challenge is that grossly normal appearing skin will microscopically be positive for AS. Intraoperative frozen sections are not reliable, with 1 series reporting that 67% of patients with AS with a negative intraoperative frozen section had positive margins on permanent section.[42] Collectively, these data show the challenge of achieving R0 surgical resection in AS. Given the high frequency of positive margins, adjuvant radiation is often reported performed after surgical resection of AS.[42]

The outcomes of head and neck AS are poor. A meta-analysis/systemic review shows the 5-year overall survival rate for AS to be between 11% and 50%.[43] Age is a major determinate of outcomes, with the 5-year overall survival for those less than 70 years of age to be 50% to 80%, whereas for those older than 70 years of age, it is reported 0% to 51%. Both Surveillance, Epidemiology, and End Results database and National Cancer Data Base studies report similar 5-year overall survival rate outcomes.[37,38]

Given the poor survival, there has been a significant interest in identifying agents that may improve survival.[44] The first line of treatment for metastatic disease has been with paclitaxel, with multiple phase II trials showing response.[45,46] Multiple agents have been tested for AS, including bevacizumab.[47] The tyrosine kinase inhibitor pazopanib has been reported, as well as propranolol and other agents.[48–51] Immune checkpoint inhibitors are currently being explored for efficacy.[52] Clinicaltrials.gov identifies at least 11 actively recruiting trials for AS, with dozens more in development.[53]

SUMMARY

Although cutaneous sarcomas are rare, awareness of these diseases is important to otolaryngologist—head and neck surgeons. An appropriate biopsy technique with careful pathologic analysis is critical to establish an accurate diagnosis. Surgical resection with adequate margins and complete histologic analysis is the gold standard for the initial treatment of most of these malignancies, per the National Comprehensive Care Network guidelines. Adjuvant therapy depends on the tumor type and its stage. Detailed understanding of the biology and nature of these cancers is important to delivering the best care. Multidisciplinary discussion should be considered for these cases.

DISCLOSURE

The authors have no conflicts of interest to disclose.

REFERENCES

1. Rouhani P, Fletcher CDM, Devesa SS, et al. Cutaneous soft tissue sarcoma incidence patterns in the U.S.: an analysis of 12,114 cases. Cancer 2008;113:616–27.

2. Bhatt MD, Nambudiri VE. Cutaneous sarcomas. Hematol Oncol Clin North Am 2019;33:87–101.
3. Kreicher KL, Kurlander DE, Gittleman HR, et al. Incidence and survival of primary dermatofibrosarcoma protuberans in the United States. Dermatol Surg 2016;42:S24–31.
4. Patel KU, Sara SS, Vivian SH, et al. Dermatofibrosarcoma protuberans COL1A1-PDGFB fusion is identified in virtually all dermatofibrosarcoma protuberans cases when investigated by newly developed multiplex reverse transcription polymerase chain reaction and fluorescence in situ hybridization assays. Hum Pathol 2008;39:184–93.
5. Rutgers Th, E J, Kroon BBR, et al. Dermatofibrosarcoma protuberans: treatment and prognosis. Eur J Surg Oncol 1992;18:241–8.
6. Meguerditchian AN, Jiping W, Bethany L, et al. Wide excision or Mohs micrographic surgery for the treatment of primary dermatofibrosarcoma protuberans. Am J Clin Oncol 2010;33:300–3.
7. Farma JM, John BA, Jonathan SZ, et al. Dermatofibrosarcoma protuberans: how wide should WE resect? Ann Surg Oncol 2010;17:2112–8.
8. Criscito MC, Martires KJ, Stein JA. Prognostic factors, treatment, and survival in dermatofibrosarcoma protuberans. JAMA Dermatol 2016;152:1365–71.
9. Bogucki B, Neuhaus I, Hurst EA. Dermatofibrosarcoma protuberans: a review of the literature. Dermatol Surg 2012;38:537–51.
10. Mentzel T, Beham A, Katenkamp D, et al. Fibrosarcomatous ('high-grade') dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. Am J Surg Pathol 1998;22:576–87.
11. Bichakjian CK, Thomas O, Murad A, et al. Dermatofibrosarcoma protuberans, version 1.2014. J Natl Compr Canc Netw 2014;12:863–8.
12. Acosta AE, Vélez CS. Dermatofibrosarcoma Protuberans. Curr Treat Options Oncol 2017;18:56.
13. NCCN, N. National Comprehensive Care Network (NCCN). Available at: https://www.nccn.org/. Accessed May 15, 2020.
14. Reha J, Katz SC. Dermatofibrosarcoma Protuberans. Surg Clin North Am 2016;96:1031–46.
15. Johnson-Jahangir H, Sherman W, Ratner D. Using imatinib as neoadjuvant therapy in dermatofibrosarcoma protuberans: potential pluses and minuses. J Natl Compr Canc Netw 2010;8:881–5.
16. Griewank KG, Bastian S, Rajmohan M, et al. TERT promoter mutations are frequent in atypical fibroxanthomas and pleomorphic dermal sarcomas. Mod Pathol 2014;27:502–8.
17. Kohlmeyer J, Steimle-Grauer SA, Hein R. Cutaneous sarcomas. J Dtsch Dermatol Ges 2017;15:630–48.
18. Mentzel T, Requena L, Brenn T. Atypical Fibroxanthoma Revisited. Surg Pathol Clin 2017;10:319–35.
19. Soleymani T, Tyler Hollmig S. Conception and management of a poorly understood spectrum of dermatologic neoplasms: atypical fibroxanthoma, pleomorphic dermal sarcoma, and undifferentiated pleomorphic sarcoma. Curr Treat Options Oncol 2017;18:50.
20. Ziemer M. Atypical fibroxanthoma. J Dtsch Dermatol Ges 2012. https://doi.org/10.1111/j.1610-0387.2012.07980.x.
21. Sandhu N, Sauvageau AP, Groman A, et al. Cutaneous leiomyosarcoma: a SEER database analysis. Dermatol Surg 2020;46:159–64.

22. Annest NM, Grekin SJ, Stone MS, et al. Cutaneous leiomyosarcoma: a tumor of the head and neck. Dermatol Surg 2007;33:628–33.
23. Bernstein SC, Roenigk RK. Leiomyosarcoma of the skin. Treatment of 34 cases. Dermatol Surg 1996;22:631–5.
24. Fields JP, Helwig EB. Leiomyosarcoma of the skin and subcutaneous tissue. Cancer 1981;47:156–69.
25. Kaddu S, Beham A, Cerroni L, et al. Cutaneous leiomyosarcoma. Am J Surg Pathol 1997;21:979–87.
26. Jensen ML, Jensen OM, Michalski W, et al. Intradermal and subcutaneous leiomyosarcoma: a clinicopathological and immunohistochemical study of 41 cases. J Cutan Pathol 1996;23:458–63.
27. Zacher M, Markus VH, Titus JB, et al. Primary leiomyosarcoma of the skin: a comprehensive review on diagnosis and treatment. Med Oncol 2018;35:135.
28. Pisters PWT, Raphael EP, Valerae OL, et al. Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas. Ann Surg 2007;246:675–81.
29. Starling J, Coldiron BM. Mohs micrographic surgery for the treatment of cutaneous leiomyosarcoma. J Am Acad Dermatol 2011;64:1119–22.
30. Von Mehren M, Cathryn R, John RG, et al. Phase 2 Southwest Oncology Group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. Cancer 2012;118:770–6.
31. Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database. Otolaryngol Head Neck Surg 2014;151:627–33.
32. Lindford A, Böhling T, Vaalavirta L, et al. Surgical management of radiation-associated cutaneous breast angiosarcoma. J Plast Reconstr Aesthet Surg. 2011;64:1036–42.
33. Farzaliyev F, Hamacher R, Steinau Professor HU, et al. Secondary angiosarcoma: a fatal complication of chronic lymphedema. J Surg Oncol 2020;121:85–90.
34. Shustef E, Kazlouskaya V, Prieto VG, et al. Cutaneous angiosarcoma: a current update. J Clin Pathol 2017;70:917–25.
35. Antonescu C. Malignant vascular tumors-an update. Mod Pathol 2014;27:S30–8.
36. Deyrup AT, McKenney JK, Tighiouart M, et al. Sporadic cutaneous angiosarcomas: a proposal for risk stratification based on 69 cases. Am J Surg Pathol 2008;32:72–7.
37. Chang C, Peter Wu S, Kenneth H, et al. Patterns of care and survival of cutaneous angiosarcoma of the head and neck. Otolaryngol Head Neck Surg 2020;162:881–7.
38. Conic RRZ, Giovanni D, Alice F, et al. Incidence and outcomes of cutaneous angiosarcoma: a SEER population-based study. J Am Acad Dermatol 2020. https://doi.org/10.1016/j.jaad.2019.07.024. 1–8.
39. Guadagnolo BA, Gunar KZ, Dejka A, et al. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. Head Neck 2011;33:661–7.
40. Constantinidou A, Nicolas S, Silvia S, et al. Evaluation of the use and efficacy of (neo)adjuvant chemotherapy in angiosarcoma: a multicentre study. ESMO Open 2020;5:e000787.
41. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 2008;44:2433–6.
42. Pawlik TM, Augusto FP, Cornelius JM, et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 2003;98:1716–26.

43. Shin JY, Roh SG, Lee NH, et al. Predisposing factors for poor prognosis of angiosarcoma of the scalp and face: systematic review and meta-analysis. Head Neck 2017;39:380–6.
44. Ishida Y, Otsuka A, Kabashima K. Cutaneous angiosarcoma: update on biology and latest treatment. Curr Opin Oncol 2018;30:107–12.
45. Penel N, Binh NB, Jacques-Olivier B, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. J Clin Oncol 2008;26:5269–74.
46. Sikov WM, Donald AB, Charles MP, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13–21.
47. 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. Available at: https://pubmed.ncbi.nlm.nih.gov/22910841/.
48. Kollár A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC soft tissue and bone sarcoma group (STBSG) retrospective analysis. Acta Oncol (Madr) 2017;56:88–92.
49. Patienten S, Therapie N. PAKT inhibitor may promote better responses to abiraterone in mCRPC. Onclive 2020;7:1–7.
50. Pasquier E, Nicolas A, Janine S, et al. Effective management of advanced angiosarcoma by the synergistic combination of propranolol and vinblastine-based metronomic chemotherapy: a bench to bedside study. EBioMedicine 2016;6:87–95.
51. Chow W, et al. Growth attenuation of cutaneous angiosarcoma with propranolol-mediated β-blockade. JAMA Dermatol 2015;151:1226–9.
52. Florou V, Wilky BA. Current and future directions for angiosarcoma therapy. Curr Treat Options Oncol 2018;19:14.
53. Available at: clinicaltrials.gov; www.clinicaltrials.gov. Accessed May 15, 2020.