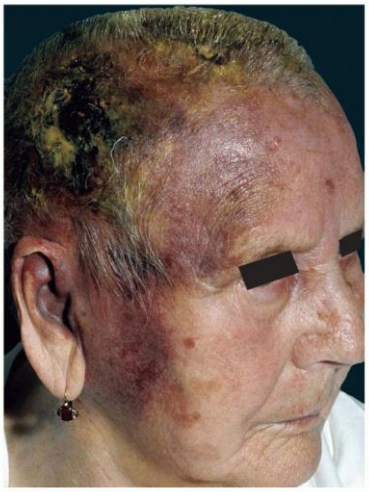
Cancer Association of South Africa (CANSA)

Fact Sheet on Angiosarcoma

Introduction

Cancerous (malignant) tumours of the connective tissues are called "sarcomas". The term sarcoma comes from a Greek word meaning fleshy growth. Normal connective tissue include, fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.

Sarcomas are divided into two main groups, bone sarcomas and soft tissue sarcomas. They are further sub-classified based on the type of presumed cell of origin found in the tumour.



[Picture Credit: Angiosarcoma]

Soft Tissue Sarcoma - is a rare form of cancer. It comprises approximately one percent of all cancers diagnosed. Slightly more men than women develop soft tissue.

Bone Sarcoma - the second group of sarcoma is bone sarcomas or bone cancer. There are three types of bone sarcoma: osteosarcoma; Ewing's sarcoma; and chondrosarcoma. Bone sarcomas are very rare.

Angiosarcoma

Angiosarcoma is a cancer of the inner lining of blood vessels, and it can occur in any area of the body. The disease most commonly occurs in the skin, breast, liver, spleen, and deep tissue. Angiosarcomas occur in men and women of all races, and are rare in children.

Spiker, A.M., Mangla, A. & Ramsey, M.L. 2020.

"Angiosarcoma (AS) comprises 1% of all soft-tissue sarcoma (STS), which are themselves a rare malignancy. They arise from lymphatic or vascular endothelial cells and are 'high-grade' by definition, which demonstrates their aggressive behavior. Although AS can occur in any part of the body, it most commonly presents as a cutaneous disease in elderly white men or on the chest wall after receiving radiation therapy (RT) for breast cancer. The treatment is very challenging, and the

prognosis is poor, especially if AS is diagnosed in the metastatic stage. The best approach to patients with AS is offered in a multidisciplinary tumor board setting. Like any other STS, surgical resection with a negative margin affords the best outcomes in terms of overall survival. Combining radiation therapy (RT) with weekly paclitaxel has been demonstrated to bear durable responses for cutaneous angiosarcoma. Doxorubicin and paclitaxel are recommended regimens for advanced or metastatic disease. Due to the increased vascularity of AS, targeted therapy against vascular endothelial growth factor (VEGF) has gained traction, however, yet remains to be proven in a prospective study."

Drosos, E., Kalvvas, A., Komaitis, S., Skandalakis, G.P., Kalamatianos, T., Liouta, E., Neromyliotis, E., Alexiou, G.A., Stranjalis, G. & Koutsarnakis, C. 2019.
"Angiosarcoma-related cerebral metastases have only been recorded in a few case reports and case series and have not been systematically reviewed to date. Our objective was therefore to perform a systematic literature review on cases of angiosarcomas metastasizing to the brain to inform current practice. All three major libraries-PubMed/MEDLINE, Embase, and Cochrane-were systematically searched, until January 2019. Articles in English reporting angiosarcoma-related cerebral metastases via hematogenous route were included. Our search yielded 45 articles (38 case reports, 5 retrospective studies, 1 case series and 1 letter to the editor), totaling 48 patients (mean age 47.9 years). The main primary site was the heart. The mean time of diagnosis of cerebral metastases following primary tumor identification was 4.9 months. In 15 cases, the brain was the only metastatic site. In cases of multiple extracerebral metastases, the most common sites were the lung and bone. Acute intracerebral supratentorial hemorrhage was the most common presenting radiological feature. Treatment strategies were almost equally divided between the surgical (with or without adjuvant treatment) and the medical arm. Mean overall survival was 7.2 months while progression-free survival was 1.5 months. To our knowledge, this is the first systematic literature review on angiosarcoma-related cerebral metastases. This pathology proves to be an extremely rare clinical entity and carries a poor prognosis, and no consensus has been reached regarding treatment."

Spiker, A.M. & Ramsey, M.L. 2019.
"Cutaneous angiosarcoma is an uncommon malignant tumor of vascular endothelial cells that most often affects the elderly and has a very poor prognosis. Although it may affect any area of the body, the most common areas of involvement are the face and scalp. Surgical excision, often followed by high-dose radiotherapy, represents the current standard of care, but recurrence remains frequent, and many patients develop the systemic disease. The cytotoxic chemotherapy effects partial response in metastatic disease, but is far from optimal. Targeted therapy with inhibitors of vascular epithelial growth factor (VEGF) and its receptor (VEGFR), or with tyrosine kinase inhibitors, has shown some efficacy and agents of this type may represent some promise for the future in treating this condition."

Incidence of Angiosarcoma in South Africa
The outdated National Cancer Registry (2017), known for under reporting, does not make mention of the incidence of Angiosarcoma.

Causes of Angiosarcoma

The most widely known cause of Angiosarcoma is lymphoedema, the swelling of an area of the body due to the collection of lymphatic fluid. Angiosarcoma can also occur due to radiation exposure or treatment, and angiosarcoma has been associated with carcinogens such as vinyl chloride, arsenic and thorium dioxide.

Cooper, H., Farsi, M., DO, D.D. & DO, R.M. 2019.

"Angiosarcomas are malignant neoplasms arising from endothelial cells. Cutaneous angiosarcoma is the most common form, typically occurring in the setting of chronic lymphedema or previous radiation. The head and neck are the most common locations for cutaneous angiosarcoma, with rare occurrence on the trunk and extremities. Herein, we present a case of angiosarcoma on the lower extremity in an elderly man. This 71-year-old man presented with a two-year history of red-yellow discoloration of the left lower leg with subsequent development of black nodules over the past several months prior to presentation. He denied any itching, bleeding, or ulceration. Past medical history included diabetes, hypertension, and non-melanoma skin cancer. Physical examination showed erythematous, violaceous, non-blanchable papules with yellow atrophic regions and overlying black crusted nodules and plaques. Biopsies were taken and the patient was diagnosed with angiosarcoma and referred to a tertiary care center for further evaluation."

Bonito, F.J.P., Cerieira, D. de A., Dahlstedt-Ferreira, C., Coelho, H.O. & Rosas, R. 2019.

"Angiosarcoma is a rare, aggressive malignant vascular neoplasm with poor prognosis that has a predilection for skin and superficial soft tissue. It can arise spontaneously or in association with factors like chronic lymphedema or radiation therapy. Radiotherapy used to treat invasive breast tumors is a known risk factor for the development of the so-called radiation-induced angiosarcoma (RIAS), a condition that has been described in the literature with increasing frequency. Radiation-induced angiosarcoma of the breast usually arises on the previously irradiated skin area several years after radiotherapy and presents as painless multifocal erythematous patches or plaques similar to a hematoma. Cutaneous biopsy is essential for the diagnosis. Histologically, RIAS is characterized by irregular anastomosing vessels lined by endothelial cells showing nuclear atypia. Treatment is mostly surgical, and mastectomy with negative margins is considered the standard procedure. However, recurrences are common, and an approach combining surgery, chemo- and radiotherapy may be more effective. The purpose of this study is to review the most recent medical literature on RIAS of the breast, with emphasis on its pathophysiology, clinical and histological features and current treatment options."

Signs and Symptoms of Angiosarcoma

The signs and symptoms of Angiosarcoma differ according to the location of the tumour. Often symptoms of the disease are not apparent until the tumour is well advanced.

Diagnosis of Angiosarcoma

Angiosarcoma is usually diagnosed following observations of where in the body it occurs.

The list of signs and symptoms mentioned in various sources for Angiosarcoma includes the listed below:

- Asymptomatic (absence of symptoms) in early stages
- Skin bruising
- Dyspnoea (difficulty breathing) - lung tumour
- Skin lesions
- Fatigue (experiencing a sensation of tiredness, weariness, exhaustion, weakness, or low energy)
- Bone pain
- Anaemia
- Skin swelling
- General pain (where it occurs in the body, e.g. abdominal pain; back pain, eye pain; headache; leg pain; jaw pain; side pain)
- Enlarged lymph nodes
- Palpable breast lump
- Unexplained weight loss
- Abnormal bleeding
- Gastrointestinal bleeding
- Chest pain - lung tumour
- Bloody sputum - lung tumour
- Cough - lung tumour

Kiyohara, M., Aoi, J., Kajihara, I., Otuka, S., Kadomatsu, T., Fukushima, S. & Ihn. H. 2020.
"There is no biomarker for detecting the status of angiosarcoma patients. Studies have reported that serum anti-p53 antibody (Ab) levels are often high in patients with various types of malignant tumors, suggesting the potential use of this Ab as a biomarker for various tumors, including angiosarcoma. The aim of this study was to assess the usefulness of serum anti-p53 Ab as a potent angiosarcoma biomarker. Nineteen angiosarcoma patients were included. All patients had histologically been diagnosed with cutaneous angiosarcoma. We compared p53 protein expression and serum p53 Ab levels between angiosarcoma in the scalp patients (n = 19) and normal controls (n = 30). We evaluated Ab levels before and after therapy. Increased p53 expression was detected in angiosarcoma skin tissues compared with that observed in normal skin tissues. We evaluated serum from angiosarcoma patients and controls for the presence of the anti-p53 Ab. Serum anti-p53 Ab levels were significantly higher in angiosarcoma patients than in controls. Serum anti-p53 Ab levels of patients who showed disease progression after therapy increased in correlation with the medical condition. The Ab levels of three patients, who showed partial response after therapy, decreased in correlation with the medical condition. The Ab levels of the other three patients were low at all time points. Anti-p53 Ab levels were significantly higher in angiosarcoma patients than in the controls. We demonstrated that serum anti-p53 Ab levels would reflect the clinical course of angiosarcoma patients, suggesting that serum anti-p53 Ab can be a potent diagnostic and prognostic biomarker of angiosarcoma."

Cao, J., Wang, J., He, C. & Fang, M. 2019.
"Angiosarcoma is a highly malignancy of endothelial tumor and represents 1-2% of all soft tissue sarcomas in humans. The aetiology of angiosarcoma is not clear but there are definite risk factors including chronic lymphoedema, history of radiation, environmental carcinogens and certain familial syndromes. Ultrasound, CT and MR are diagnostic tools, but final diagnosis requires pathological and immunohistochemical confirmation. The conventional options of treatment include surgery, radiotherapy and chemotherapy. Targeted medicines and immunotherapy have been studied as promising treatment of angiosarcoma. The goal of this review is to summarize the current data

regarding of angiosarcoma and its clinical presentation and management, providing a useful clinical tool to explore the optimal treatment."

Treatment of Angiosarcoma

Treatment of Angiosarcoma is dependent on the location and the extent of the tumour. Treatment may include:

- Chemotherapy
- Surgery
- Radiotherapy
- Anti-angiogenic therapy
- Targeted therapy
- Or a combination of two or more the above treatment modalities.

Spiker, A.M., Mangla, A. & Ramsey, M.L. 2020.

"Angiosarcoma (AS) comprises 1% of all soft-tissue sarcoma (STS), which are themselves a rare malignancy. They arise from lymphatic or vascular endothelial cells and are 'high-grade' by definition, which demonstrates their aggressive behavior. Although AS can occur in any part of the body, it most commonly presents as a cutaneous disease in elderly white men or on the chest wall after receiving radiation therapy (RT) for breast cancer. The treatment is very challenging, and the prognosis is poor, especially if AS is diagnosed in the metastatic stage. The best approach to patients with AS is offered in a multidisciplinary tumor board setting. Like any other STS, surgical resection with a negative margin affords the best outcomes in terms of overall survival. Combining radiation therapy (RT) with weekly paclitaxel has been demonstrated to bear durable responses for cutaneous angiosarcoma. Doxorubicin and paclitaxel are recommended regimens for advanced or metastatic disease. Due to the increased vascularity of AS, targeted therapy against vascular endothelial growth factor (VEGF) has gained traction, however, yet remains to be proven in a prospective study."

Sturm, E., Marasco, I.S. & Katz, S.C. 2020.

"Angiosarcomas (AS) are a diverse group of soft tissue sarcomas, arising from blood and lymphatic vessels. They frequently present in the elderly, and in patients with previous radiation or lymphedema. A wide range of genetic derangements contribute to their development, and AS histology is often high-grade in keeping with aggressive disease biology. The clinical presentation, while often innocuous, is marked by its infiltrative and aggressive nature, with a proclivity for metastatic spread, and outcomes are often poor. Surgery is performed for localized, resectable cases. A multidisciplinary approach, appropriately employing surgery, radiation, chemotherapy, or potentially recently approved immune-oncology agents, can result in positive outcomes."

Bönisch, N., Langan, E.A. & Terheyden, P. 2019.

Background: Whilst cutaneous angiosarcoma is rare tumour which primarily affects elderly patients, its management presents a significant therapeutic challenge. Indeed, complete surgical excision is often not possible due to the location and the diffuse and extensive nature of the tumour. Therefore, current treatment strategies often include chemo- and/or radiotherapy.

Methods: We report our experience of combined chemo- and radiotherapy in the clinical course of 6 patients with cutaneous angiosarcoma who were treated between 2007 and 2018.

Results: All patients presented non-resectable tumours and were treated with radiotherapy in combination with the administration of liposomal, pegylated doxrubicin (25 mg/m^2 every 2 weeks). The mean duration of progression-free survival was 8 months (5-14 months), corresponding to an

overall survival of 13 months (13-34 months). A partial response was seen in 4 patients and 1 patient developed progressive disease. One patient abandoned therapy after one administration. Two patients developed severe adverse events which led to termination of therapy after 1.5 months and 7 months, i.e. after 4 and 15 cycles respectively.
Discussion: Combined radio- and chemotherapy with liposomal, pegylated doxorubicin is a useful therapeutic option in the management of cutaneous angiosarcoma. Given the short-lived response rate, new treatment options are urgently required.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

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Sources and References Consulted or Utilised

Angiosarcoma
http://www.dermaamin.com/site/atlas-of-dermatology/1-a/105-angiosarcoma-

Bönisch, N., Langan, E.A. & Terheyden, P. 2019. Cutaneous angiosarcoma: radiochemotherapy with liposomal pegylated doxorubicin. *Hautarzt*, 70 (9), 700-706. Sep 2019.

Bonito, F.J.P., Cerieira, D. de A., Dahlstedt-Ferreira, C., Coelho, H.O. & Rosas, R. 2019. Radiation-induced angiosarcoma of the breast: a review. *Breast J,* 2019 Aug 25[Online ahead of print].

Cancer Wall
https://cancerwall.com/angiosarcoma-prognosis-symptoms-treatment-pictures-causes/

Cao, J., Wang, J., He, C. & Fang, M. 2019. Angiosarcoma: a review of diagnosis and current treatment. Am J Cancer Res, 9 (11), 2303-2313. 2019 Nov 1 eCollection 2019.

Cooper, H., Farsi, M., DO, D.D. & DO, R.M. 2019. Cutaneous angiosarcoma of the leg. *Dermatol Online* J, 25 (12). 2019 Dec 15.

DermNet New Zealand
https://www.dermnetnz.org/topics/angiosarcoma/

Drosos, E., Kalvvas, A., Komaitis, S., Skandalakis, G.P., Kalamatianos, T., Liouta, E., Neromyliotis, E., Alexiou, G.A., Stranjalis, G. & Koutsarnakis, C. 2019. Angiosarcoma-related cerebral metastases: a systematic review of the literature. *Neurosurg Rev*, 2019 Jun 4[Online ahead of print].

Ishida, Y., Otsuka, A. & Kabashima, K. 2017. Cutaneous ahgiosarcoma: update on biology and latest treatment. *Curr Opin Oncol*. 2017 Dec 13. doi: 10.1097/CCO.0000000000000427. [Epub ahead of print]' PMID: 29194075.

Kiyohara, M., Aoi, J., Kajihara, I., Otuka, S., Kadomatsu, T., Fukushima, S. & Ihn. H. 2020. Serum anti-p53 autoantibodies in angiosarcoma. *J Dermatol*. 2020 Aug;47(8):849-854.

Matti, A., Farolfi, A., Frisoni, T., Fanti, S. & Nanni, C. 2018. FDG-PET/CT guided biopsy in angiosarcoma of bone: diagnosis, staging and beyond. *Clin Nucl Med*. 2018 Feb;43(2):e48-e49. doi: 10.1097/RLU.0000000000001918. PMID: 29215413.

Medscape
http://emedicine.medscape.com/article/276512-differential

PDQ Pediatric Treatment Editorial Board. 2002 – 2017. Childhood soft tissue sarcoma treatment (PDQ®): health professional version. PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. 2017 Dec 6. PMID: 26389361.

Moon, S.Y., Eun, D.H., Jang, Y.H., Lee, S.J., Kim, D.W., Lee & W.J. 2017. Primary angiosarcoma of the skin presenting as mild erythaema. *Ann Dermatol*. 2017 Dec;29(6):809-810. doi: 10.5021/ad.2017.29.6.809. Epub 2017 Oct 30. No abstract available. PMID: 29200779.

Right Diagnosis
http://www.rightdiagnosis.com/a/angiosarcoma/symptoms.htm

Sarcoma Alliance
http://sarcomaalliance.org/what-you-need-to-know/bone-sarcoma/

Sarcoma Foundation of America
http://www.curesarcoma.org/patient-resources/sarcoma-subtypes/angiosarcoma/

Spiker, A.M., Mangla, A. & Ramsey, M.L. 2020. Angiosarcoma. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Oct 7.

Spiker, A.M. & Ramsey, M.L. 2019. Cancer, angiosarcoma. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. 2019 Feb 21.

Sturm, E., Marasco, I.S. & Katz, S.C. 2020. Multidisciplinary management of angiosardoma – a review. J Surg Res. 2021 Jan;257:213-220.

The Liddy Shriver Sarcoma Initiative
http://sarcomahelp.org/angiosarcoma.html

Young, R.J. & Woll, P.J. 2017. Anti-angiogenic therapies for the treatment of angiosarcoma: a clinical update. *Memo*. 2017;10(4):190-193. doi: 10.1007/s12254-017-0365-x. Epub 2017 Nov 7. Review. PMID: 29250195.

Young, R.J., Brown, N.J., Reed, M.W., Hughes, D. & Woll, P.J. 2010. Angiosarcoma. *Lancet Oncol*. 2010 Oct;11(10):983-91. doi: 10.1016/S1470-2045(10)70023-1. Epub 2010 May 25.