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\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0,0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

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S1-Guideline Cutaneous Angiosarcomas – Update 2021

Guideline on behalf of the Working Group for Dermatological Oncology (Arbeitsgemeinschaft Dermatologische Onkologie, ADO) of the German Cancer Society (Deutsche Krebsgesellschaft, DKG) and the German Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG)

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1. Scope

This guideline focusses on malignant cutaneous angiosarcomas including angiosarcomas arising from chronic lymphedema and angiosarcomas after irradiation. Basically, any organ (such as the heart, aorta, or liver) can be the site of origin of primary angiosarcoma – however, these are not the subject of this guideline. A synopsis of the salient points of the guideline can be found in the online supplement, Table 11. The references are also listed in the online supplement.

2. Epidemiology

About 1 % of all cancers are sarcomas. Angiosarcoma (AS) is a very rare malignant tumor, originating from vascular endothelial cells and accounting for about 1–2 % of all soft tissue sarcoma. It is estimated that about forty to fifty cases are diagnosed in Germany each year (see www.krebsdaten.de, data from GEKID [Gesellschaft der epidemiologischen Krebsregister e.V., Society for epidemiological Cancer Registries] and ZfKD [Zentrum für Krebsregisterdaten, Robert Koch Institute).

The proportions of incidence for all sarcomas are estimated as follows: Rouhani et al. [1] investigated the incidence of cutaneous soft tissue sarcomas in the USA over a period of 12 years (1992–2004). Of 12,114 cases, Kaposi's sarcoma was represented with 71.1 %, mostly associated with HIV. AS with 1.6 % was the fourth most common sarcoma, after dermatofibrosarcoma protuberans (1.4 %), malignant fibrous histiocytoma (5.3 %), and leiomyosarcoma (2.2 %). All other sarcoma entities affecting the skin are even rarer than AS. Due to the clinical risk of confusion with other diagnoses, cutaneous angiosarcoma, as the fourth most common sarcoma of the specialty, is very much a relevant disease for dermatologists. In addition, secondary AS of the breast is becoming more prevalent due to radiotherapy after

breast-preserving surgery for mammary carcinoma.

The superficial soft tissues of the head, neck and scalp are the predilection sites for AS with about 60 % of cases. The sex ratio is 2 : 1, men to women, and the average age for typical superficial-cutaneous AS is 65 to 70 years. Primary AS of the breast in women not exposed to radiotherapy, as well as AS of deep soft tissue and inside the body, may, however, also affect younger patients. In childhood and adolescence, AS may in rare cases affect internal organs [2].

Hemangioendotheliomas (kaposiform hemangioendothelioma, endovascular papillary angioendothelioma Dabska, retiform hemangioendothelioma, pseudomyogenic hemangioendothelioma, epithelioid hemangioendothelioma, composite hemangioendothelioma) are nowadays classified as low grade or intermediary-malignant vascular tumors of the skin – meaning they may well display localized, aggressive growth and frequent recurrence. Metastases are less common and mostly affect the local lymph nodes. Dabska tumors and kaposiform hemangioendothelioma are mainly found in children, and others such as malignant epithelioid hemangioendotheliomas may also be found during childhood. In contrast, high grade vascular tumors of the skin mainly affect adults and the elderly, including classic AS on the head in elderly patients, AS with lymphedema, AS after irradiation of the skin, and epithelioid AS [3].

3. Risk factors

The largest proportion (about two-thirds) of primary cutaneous AS appears to be located in the head and neck region, followed by the lower arms and legs. The reasons for this fact are currently unknown; it has not been established if UV exposure may be a relevant risk factor for AS. We therefore cannot state if sunscreen may have a preventative role [4].

Secondary AS after radiation therapy within the framework of breast-preserving treatment of mammary carcinoma is an increasingly relevant problem. Whereas in the past radiogenic angiosarcomas were predominantly found in the abdominal region, for example after radiotherapy of the cervix, the ovaries or the uterus, today they are mainly a complication after adjuvant radiotherapy of the mammary glands. Induction of AS via ionizing radiation *per se*, without lymphedema, is an established fact. The mean latency after irradiation of a tumor is 4–8 years. The cumulative incidence for the breast is 0.9 per thousand treated patients. Thus, the prognostic benefit of adjuvant irradiation of the breast after breast-preserving surgery is orders of magnitude higher than the risk of AS for most patients [5–16].

In cases of breast-preserving cancer treatment with adjuvant radiation therapy (RT), other risk factors may contribute to the general risk of radiation. These include lymphedema and occasionally also predisposing gene defects such as the DNA repair genes *BRCA1* and *BRCA2* [16, 17]. This is plausible from a molecular genetic point of view, since as opposed to translocation and gene fusion sarcomas such as clear cell sarcoma or dermatofibrosarcoma protuberans (DFSP), AS belongs to the group of sarcomas with complex chromosomal damage. Single mutations (quite frequently *PT53* 30 %, *PTRB* 25 %) and (expression) genetic findings such as MAPK signal pathway dysfunction or expression of HSP90, FOXM1, miR-4975p, miRNA210, may indicate new therapeutic target structures. They each represent comparatively small subgroups, and the general situation is very heterogeneous. New therapeutic options are emerging, but these will require a high degree of individualization or precision medicine (overview: [18]).

Persistent lymphedema is another known risk factor for AS. This usually affects women with radical mastectomy and axillar lymph node dissection for breast cancer, after long-term lymphedema. The disease, known as Stewart-Treves syndrome, has become quite rare (about 5 % of AS). Latency is 10 to 15 years after surgery, and prognosis is bad with an overall survival after five years of only about 15 % [19, 20]. All other forms of lymphedema including congenital forms are only rarely found to constitute a promoting factor. Interestingly, AS almost never arise from the relatively common hemangiomas and vascular malformations. Thus, AS in Klippel-Trenaunay syndrome or childhood hemangiomas are a rarity [21, 22]. An AS origin in other benign tumors such as leiomyoma [23] or neurofibroma [24] is also very rare.

Arteriovenous fistulas may also promote AS, for example on the shunt arm especially after dialysis, in patients with renal transplants and immunosuppression [25, 26]. The role of immunosuppression for AS has not yet been fully clarified but appears to be relevant. The role of carcinogens and foreign bodies (such as tattoo inks) for cutaneous AS is also still unclear. We do know that thorotrast, arsenic, anabolic steroids, and vinyl chloride play a causal role in the liver. A connection of AS with human herpes virus 8 (HHV-8) has been convincingly excluded, whereas Kaposi's sarcoma is 100 % associated with HHV-8 [27].

4. Prevention

To reduce the risk of epithelial tumors, patients are counseled to limit UV exposure. This can also be recommended for AS. Other preventative measures are not known.

5. Screening

Since cutaneous AS are so rare, general screening is not recommended. Specialists, primarily dermatologists and gynecologists, should be aware of this serious differential diagnosis even in view of the mostly non-specific early clinical

presentation and possibly less than alarming PE histology (for example "benign lymphangioma" as opposed to highly differentiated AS). Multiple biopsies may be required, and in cases of doubt, R0 excision and radiotherapy must be undertaken.

6. Primary diagnostics

Clinical examination – clinical findings

The first challenge in diagnosing AS is to be aware of this rare disease, and the second is to confirm the diagnosis via histopathology. Careful inspection is the most important tool in clinical examination. The following clinical characteristics need to be noted [2, 3]:

Typical cutaneous AS (the most common form at about 60 %): This type of AS is seen mostly on the head and neck of older patients, with a clear preponderance of males (sex ratio 2 : 1 male to female). Contusiform erythema in skin areas exposed to light or on the capillitium may constitute the only clinical signs of early disease (Figure 1). Some cases show a dusky-red margin with fresh hemorrhaging into the skin, "like ink being soaked up by blotting paper". Due to the non-specific clinical appearance, delayed diagnosis is a common problem, as well as misdiagnoses such as "unclear inflammatory facial dermatosis", "unclear persisting rosacea", or erysipelas, urticarial vasculitis, granuloma faciale, lupus erythematosus, posttraumatic hematoma, or contusion.

Filling and better visibility of the erythema after ten seconds of lower positioning of the head (head tilt maneuver according to [28]) is an important clinical sign.

Edematous swelling and facial hematomas, nodular plaques, plate-like palpatory findings, or ulcerating and bleeding tumors that may be extensive, are all localized findings in the late stage, mostly found in recurrent tumors. The recurrences as such (two-thirds) and the metastases (one-third, mostly pulmonary) constitute the most common causes of death due to this tumor, mainly due to uncontrollable bleeding.

Cutaneous AS after radiotherapy must be differentiated from atypical vascular lesions (AVL) after radiotherapy, clinically and histologically. AVL usually present as small (< 1 cm), cystic nodules, not hemorrhagic but pink to glassy, similar to frog spawn.

As opposed to these benign AVL, AS of the irradiated breast shows non-specific skin symptoms with hematoma-like, contusiform erythema. Palpable tumors appear later.

AS of non-irradiated breasts occurs only in women, mostly in the 3rd and 4th decade of life; this constitutes only 1–2 per mille of all malignant breast tumors. Large case collections have confirmed that patients with AS in non-irradiated breasts are much younger than women with previously irradiated breast tissue. The clinical appearance is also different, with palpable circumscribed dense tissue. The surface of the skin is not always affected.

Some experts doubt that non-irradiated healthy breast tissue *per se* is a risk area for AS and that it actually shows a significantly higher AS incidence than other regions of the skin.

Lymphedema-associated AS according to Stewart and Treves should be considered if dusky, contusiform lesions appear within the lymphedema. Biopsies are mandatory, and evaluating the histology may be challenging (see next chapter).

Subjective symptoms are usually absent in all forms of AS for a long time. Pain is not an early warning sign. One dreaded feature is angiocentric and angiooccclusive tumor growth, which is especially characteristic for epithelioid angiosarcoma. This leads to ischemic pain that is difficult to manage.

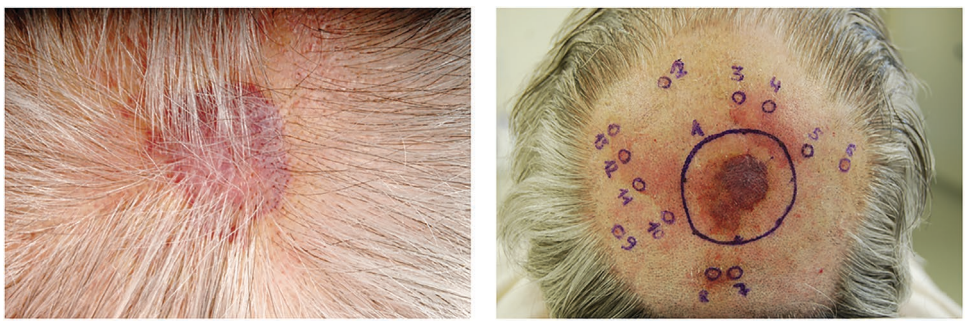

Figure 1 Two thirds of the cutaneous angiosarcomas occur in the head and neck area. The clinical appearance is unspectacular and not specific. This may lead to incorrect diagnosis and delay. Left, finding on the capillitium, a red macule. Right, after shaving and head tilt maneuver the advanced locoregional extension of the angiosarcoma is clearly visible. Skip lesions can be seen in the periphery.

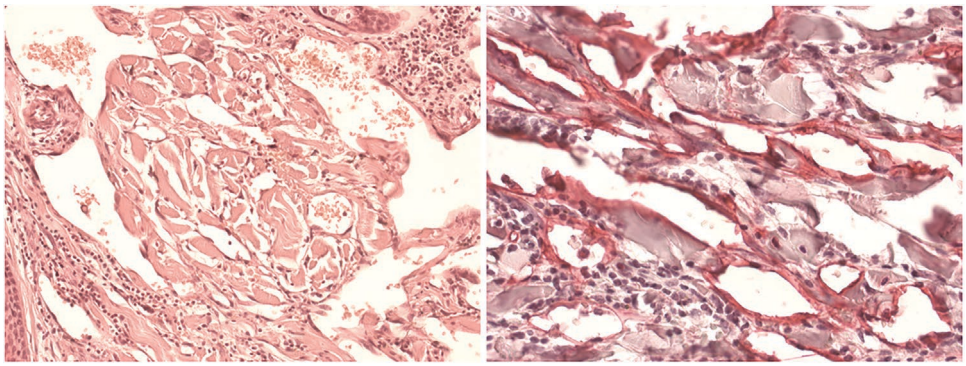

Figure 2 The diagnosis is made on the basis of histology and immunohistochemistry. Right, in hematoxylin-eosin (HE) staining dissecting diffusely growing pseudovascular spaces can be observed, they often lack blood. The endothelial cells show only limited atypia. Right, the endothelial cells express a lympho-endothelial phenotype, here podoplanin staining is positive.

Diagnostic imaging

Metastases spread to the lymph nodes, the lungs, the liver, and the spleen (with decreasing frequency). Clinically, remote metastases will thus usually present with pulmonary symptoms such as effusion, cough, hemoptysis, and shortness of breath.

Propagation diagnostics for AS requires individualized use of diagnostic imaging: lymph node sonography, computed tomography (CT), or alternatively magnetic resonance imaging (MRI). PET CT may offer important additional information including the extent in the soft tissue mantle of the skin, which is useful for surgery planning [29–31].

7. Histopathology and molecular diagnostics

Since early clinical findings are non-specific and subtle, a biopsy should be taken even at the slightest suspicion of AS; where necessary even multiple times. Typical cutaneous AS are superficial, yet the biopsy should extend into the subcutaneous fatty tissue.

Histopathologically and also ultrastructurally, angiosarcomas consist of proliferating, usually atypical endothelia. The degree of differentiation varies widely, from lymphangioma/hemangioma-like to markedly anaplastic forms. The latter show some morphological analogies to carcinomas or melanomas, which have contributed to misleading "synonyms".

Angiosarcoma cells mostly form vessel-like structures, though with a tendency to develop bizarre, dissecting networks with anastomoses without following any given structures. Histology shows that these networks are conspicuously bloodless, which differentiates them, for example, from Kaposi's sarcoma. Multilayering, atypia, and endothelial mitoses complete the histological picture but may be subtle. Endothelial cells sloughed off into the lumen are typical ("fish in the creek" sign) [3] (Figure 2).

Angiosarcomas typically express the lymphatic endothelial markers D2-40 podoplanin, LYVE-1, PROX-1 together with a αSMA-positive surrounding cell layer. Other factors such as Factor VIII, CD31 (platelet endothelial cell adhesion molecule, PE-CAM) and CD34 (human hematopoietic progenitor antigen) are also frequently positive. Strong positivity of Ki67, as well as necroses, are considered histological signs of an unfavourable prognosis.

Importantly, not all markers must be positive; therefore, panel diagnostics are required. Table 1 shows the expected values from the literature (Table 1).

In addition, transcription factors of relevance, from a developmental biology perspective, are used as AS markers, for example in diagnostically difficult situations such as aberrant co-expression of cytokeratins: *ERG* (ETS-related gene), which is currently considered the most specific and sensitive vascular marker, and *Fli-1* [32, 33].

In prognostically unfavorable epithelioid angiosarcomas, the histological picture is dominated by "lawns" of large epithelioid cells, with narrow, blood-filled slits and

Table 1 Relative frequency of expression of important markers of angiosarcoma (AS).

Antigen	Rate of positive AS
Factor VIII	83 %
CD31	80 %
CD34	63 %
D2-40	43 %

Table 2 Histopathologic criteria for differentiation of atypical vascular lesions (AVL) and angiosarcoma (AS) in irradiated skin of the breast.

Histopathological sign	AVL	AS
Infiltration of the subcutis	–	+++
Papillar, endothelial hyperplasia	–	+++
Prominent nucleoli	–	+++
Mitoses	–	+++
Cytological atypia	–	+++
Hyperchromia of endothelia	–	+++
Dissection of collagen	+/–	+++
Vascular anastomoses	++	+++
Blood lakes	–	++
Chronic inflammation	+++	+
Circumscribed growth	+++	–
Intraluminal stroma projections	+++	–

fissures between. There are many similarities with epithelial tumors. Necroses and bleeding are important secondary criteria. More than 30 % of epithelioid angiosarcomas are cytokeratin-positive; CD31, Fli-1 and ERG are then conclusive.

If immunohistological investigations have been used for differentiation, these results should be included in the report. The histological report should also contain the findings on tumor size (mm/cm) as far as recorded, as well as depth of invasion/tumorthickness, mitoses and necroses, and the TNM-relevant findings for grading.

In irradiated breast tissue, differentiating AVL (see above) from angiosarcoma may be something of a challenge. Table 2 shows the morphological criteria defined by Fineberg and Rosen for this purpose [7].

Recent investigations have found that AVL have a rate of *TP53* mutations that is similar to angiosarcoma. This suggests that the two entities may be the extremes of a spectrum of malignancy grades, with AVL at the "almost benign" end. Follow-up of AVL patients should consider this fact for individual risk assessment [13].

In radiation-induced AS, diverse genetic damage also accumulates. Increased expression of the oncogene *c-MYC* via gene amplification is a fairly consistent feature of radiation-induced AS. The amplification detected by fluorescence in situ hybridization (FISH) shows a 100 % correlation with immunohistological staining [34].

The numerous genetic aberrations in primary and radiation-induced AS play a minor role in diagnostics. Both types of sarcoma basically display a high rate of genomic alterations (see the overview in [35]): TP53, KRAS, PTPRB, and PLCG1 are frequently affected by mutation. While mutations of the tumor suppressor TP53 are relevant in many tumors, PTPRB and PLCG1 have a direct impact on angiogenesis. An additional, angiogenetically relevant fusion gene (NUP160-SCL43A3) was detected in nine out of 25 AS [36]. Primary and secondary AS appear to carry different genetic signatures: Apart from the aforementioned, diagnostically relevant differential expression or up-regulation of MYC, radiation-induced AS also show upregulation of the gene products of KIT, FLT4, and RET (among others) while CDKN2C is down-regulated [15].

TNM staging and grading

The revised AJCC Cancer Staging Manual, 8th Edition, classifies soft tissue sarcomas based on TNM and tumor grading (G). The American Joint Committee on Cancer (AJCC) has adopted the grading system published by the French Federation of Cancer Centers Sarcoma Group (FNCLCC). Tumor grading is based on cellular differentiation, mitosis rate, and extent of the necroses (Part IX Soft Tissue Sarcoma. Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8th edition. Springer International Publishing; 2017: 214–39) [37] (Tables 3–6).

Dermatooncologists should note that staging systems for AS differ depending on their location either in the head and neck region or on the trunk and limbs.

The classification for the head and neck is new (Table 4). Due to the lack of prognostic data, no prognostic groups have as yet been defined for this area.

8. Topical treatment – management of the primary tumor and of recurrent tumors

Surgery is traditionally considered the mainstay of AS treatment. Early and generous R0 resection is the goal. A German publication of 80 margin-controlled resections showed that R0 has a significant influence on overall survival as compared with R1 [38].

In practice, however, multifocal growth (skip lesions) makes histologically flawless and reliable determination of the R0 situation in all margins impossible. Grid-like biopsies may help in some cases, but the clinically visible "margins" are never truly reliable, even with meticulous processing [39].

Study data on the importance of resection status for disease-specific survival are conflicting: Whereas a single German study by Dettenborn et al. [38] based on 80 cases showed that incomplete resection was a significant predictor ($P < 0.05$) of an unfavorable prognosis for survival, data from other studies suggest that in about 25 % of operations, R0 resection

Table 3 Histologic grading of soft tissue sarcomas.

Tumor differentiation	Number of mitoses	Tumor necrosis
Sarcoma shows strong similarities to normal adult tissue (for example low-malignancy leiomyosarcoma) (1 point)	0–9 mitoses per 10 HPF (1 point)	No tumor necrosis (0 points)
Sarcoma with distinct histological typing (for example myxoid round cell liposarcoma) (2 points)	10–19 mitoses per 10 HPF (2 points)	< 50 % tumor necrosis (1 point)
Embryonal and non-differentiated sarcoma, sarcomas of questionable type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/soft tissue primitive neuroectodermal tumor (PNET) (3 points)	≥ 20 mitoses per 10 HPF (3 points)	≥ 50 % tumor necrosis (2 points)
The scores of these variables are added up, resulting in the following grades: – GX – Grade cannot be assessed – G1 – Total score 2–3 – G2 – Total score 4–5 – G3 – Total score 6 or higher		
Abbr: HPF, High Power Field.		

Table 4 TNM classification of soft tissue sarcomas in the head and neck region.

Primary tumor (T)	
TX	Primary tumor cannot be measured
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm to ≤ 4 cm
T3	Tumor > 4 cm
T4	Tumor invading surrounding anatomical structures
T4a	Tumor invating the orbita, base of the skull/dura mater, central organs of the head, the facial skull, the pterygoid muscles
T4b	Tumor invading the CNS, with the carotid sheath, invading the paravertebral muscles, or invading the CNS via perineural spreading
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
No	No nodal metastases
N1	Regional lymph node mestastases
Remote metastases (M)	
Mo	No remote metastases
M1	Remote metastases
Histological grade (G)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

Table 5 TNM classification of soft tissue sarcomas on the trunk and extremities.

Primary tumor (T)	
TX	Primary tumor cannot be measured
To	No evidence of a primary tumor
T1	Tumor ≤ 5 cm at the largest diameter
T2	Tumor > 5 cm to ≤ 10 cm at the largest diameter
T3	Tumor > 10 cm to ≤ 15 cm at the largest diameter
T4	Tumor > 15 cm at the largest diameter
Regional lymph nodes (N)	
No	No lymph node metastases, or nodal metastases cannot be assessed
N1	Regional lymph node metastases
Remote metastases (M)	
Mo	No remote metastases
M1	Remote metastases
Histological grade (G)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

cannot be achieved anyway [39] and that R0 resection does not appear to play a significant role for long-term prognosis [40]. In addition, locoregionally spread angiosarcomas frequently take a lethal course [38] even after surgery with margin control. Other authors therefore argue that attempts to achieve R0 with complex and possibly multiple operations that place a heavy burden on the patient should at least not delay any follow-up treatment procedures. In most cases, this is adjuvant radiotherapy (RT). For example, based on 70 cases, Guadagnolo et al. [40] advocate a rapid debulking of the tumor mass, using the clinical margins as a guide, with early radiotherapy as follow-up. Ultra-radical surgery and time-consuming postoperative rehabilitation should be avoided. Broad resection appears to be superior even to the even more radical surgical measures such as amputation of whole limbs, though the retrospective assessment may have been influenced by patient selection.

Table 6 TNM stages and prognostic groups, respectively (trunk and extremities).

Stage	T	N	M	Histological grade
IA	T1	No	Mo	G1, GX
IB	T2	No	Mo	G1, GX
	T3	No	Mo	G1, GX
	T4	No	Mo	G1, GX
II	T1	No	Mo	G2, G3
IIIA	T2	No	Mo	G2, G3
IIIB	T3	No	Mo	G2, G3
	T4	No	Mo	G2, G3
IV	Any T	N1	Mo	Any G
	Any T	Any N	M1	Any G

If primary wound closure is not feasible, split-skin transplants are the method of choice for covering the defect. Skin replacement procedures may speed up healing of the defect, and after the replacement has healed, radiotherapy may be initiated even before the final therapy (for example via mesh graft) [41–43]. Rotational grafts and other flaps should only be used in exceptional cases since they may impede clinical recurrence control.

Monotherapy either by surgery only or by radiotherapy only should be avoided, since multidisciplinary studies have clearly proven the value of postoperative adjuvant radiotherapy. This is associated with a significant reduction in mortality. Exclusive radiotherapy in inoperable patients, with curative intent, is associated with markedly inferior local tumor control of < 20 %, and is therefore not justified without compulsion. Whenever possible, a multimodal treatment approach with primary surgery followed by adjuvant radiotherapy should be the goal. There are no randomized controlled trials (RCT) on this topic, but a large collection of 67 cases showed that after five years, surgery plus subsequent radiotherapy showed local tumor control in 84 % of cases, which was significantly better ($P < 0.003$) than 25 % after surgery only and 22 % after radiotherapy only [40]. Irradiation of the skin should always be performed with "broad" safety margins of 3–5 cm around the defect caused by surgery, even if these margins have not yet been standardized. Adjuvant radiation in cases of assumed removal of the tumor (R0 resection) should be 55–60 Gy in amounts of 2 Gy every working day. If large areas need to be treated, the field may be decreased after 50 Gy, or alternatively a boost of 6–10 Gy as a dose escalation may be focused on the original tumor area. In cases of marginal or incomplete resection, with or without macroscopically visible residual tumor tissue, the aim should be a dose escalation above 70 Gy [44].

Modern irradiation techniques comprise intensity-modulated photon techniques, standing-wave electron fields, or image-guided brachytherapy approaches with a sufficient safety margin around the surgical defect [45, 46].

Positive data are also accumulating for *hyper*fractionated radiotherapy in radiation-induced AS of the mammary region after breast-preserving surgery [11]. Longer recurrence-free courses have been reported after neoadjuvant use with radiotherapy followed by surgery [47].

Primary radiochemotherapy

If an AS is primarily inoperable, definitive radiotherapy or if appropriate combined radio/chemotherapy, usually with taxanes, is an option. The data supporting this approach can be summarized as follows [45]: Radiotherapy with median doses of 70 Gy can achieve local tumor control in about 50 % of cases. Due to lack of data, the optimum dose has not yet been defined, so higher doses > 70 Gy may be considered for deeply infiltrating tumors to improve local tumor control. Metastases will occur in almost 50 % of patients, regardless of local tumor control. Chemotherapy, especially taxanes, can improve prognosis if administered as a neoadjuvant, simultaneously, or in post-radiotherapeutic treatment.

Neoadjuvant chemotherapy (NAC) may be considered in special situations for palliative purposes, especially to maintain organ function such as when the AS occurs near the orbita and the eye may be lost [48]. A trend towards improved survival due to neoadjuvant treatment has not so far been proven, but good response to NAC defines a subgroup with especially good local tumor control [49].

For recurrent tumors, surgical debulking or repeat R0 resection should be discussed, potentially followed by normofractionated and hyperfractionated radiotherapy or image-guided local brachytherapy prior to and along with medical systemic treatment.

9. Medical treatment of inoperable or metastasized tumors

The general value of surgery has recently been called into questioned, with the argument that patients with locoregionally advanced tumors will mostly die of the tumor sooner or later anyway, despite surgery and radiotherapy. In view of new medical compounds, primary chemotherapy or targeted therapy are being discussed, especially long-term secondary chemotherapy or targeted adjuvant treatment (maintenance therapy).

Medical adjuvant maintenance therapy, also after surgery and radiotherapy and preferably with less toxic, low-dose metronomic compounds, may be the way in the future. In 2014, for example, Fujisawa et al. [50] reported on a series of nine patients who were treated with taxanes after surgery and radiotherapy, without any deaths over a period of five years. In contrast, all of the seven patients who only received surgery and radiotherapy died within 36 months.

Table 7 Status of approval by the drug administration (Europe/Germany).

Doxorubicin/ pegylated doxorubicin	Off label
Ifosfamide	On label ("other soft tissue sarcomas")
Paclitaxel	Off label
Gemcitabine	Off label
Trabectedine	On label ("soft tissue sarcomas", second-line)
Pazopanib	On label ("soft tissue sarcomas", second-line)
Bevacizumab	Off label
Sorafenib	Off label
Trofosfamid as monotherapy and in combination with pioglitazone and coxibs	Off label
Propranolol	Off label
IL2/Interferon α	Off label
Immune checkpoint inhibitors	Off label

The value of medical treatment has not been scientifically proven so far, but positive case reports indicate a possible advantage [51, 52].

In general, on-label treatment for AS is only possible in exceptional cases, due to the rarity of the disease and the ensuing lack of pivotal studies. Physicians who treat AS patients need to be aware of this, since it influences patient information and reimbursement. Table 7 shows the approval status of medications which may be suitable for treating patients with angiosarcoma.

Chemotherapy

Apart from individual case reports, most publications on chemotherapy for inoperable AS involve pegylated liposomal doxyrubicine and paclitaxel (Table 2). As a rule of thumb, about one-quarter of patients (reports range from 17–34 %) respond to doxyrubicine-based treatment approaches. Addition of ifosfamide – based on broader experience with other soft tissue sarcomas – may improve response rates, albeit with significant added toxicity. One case series on doxyrubicine (every 28 days 50 mg/m^2; n = 6) reported two partial remissions (PR) for six and 19 months, two cases of stable disease (SD) for seven and twelve months, one case of progressive disease while on treatment, and one case of slow PR after twelve months for more than twenty months [53].

A large retrospective analysis of 125 cases showed very similar results for liposomal doxyrubicine and paclitaxel, with a median progression-free survival of 4.0 and 4.2 months, respectively. The combination of doxyrubicine and ifosfamide (with a limited number of patients) showed the longest progression-free survival at 5.4 months [54].

Newer studies are available, mostly for taxanes. In the ANGIOTAX study with 30 patients, 80 mg/m² paclitaxel were administered on days 1, 8, and 15 every four weeks, achieving a progression-free survival (PFS) of 74 % after two months and 45 % after four months [55]. Other studies support the equal value of anthracyclines and taxanes [56–58]. An EORTC study on paclitaxel showed response rates of 62 % (all AS) to 75 % (scalp) in a total of 32 patients [59]. New data by Stacchiotti et al. [60] on monotherapy with gemcitabine (1000 mg/m² per week in weeks 1–3, every four weeks) are also of interest; the rate of complete plus partial remission was 68 %.

New targeted treatment options

Two new targeted therapies have recently been approved for second-line treatment of advanced sarcomas. In principle, they can also be used for advanced AS.

Trabectedin, Ecteinascidin-743

Trabectedin is a compound found in tunicates (*ecteinascidia turbinata*, sea squirts). Its antitumor potential is based on anti-inflammatory and anti-angiogenetic partial mechanisms as well as cytostatic effects (such as DNA double-strand breakage). The substance has been approved for the treatment of adult patients with advanced soft-tissue sarcoma after other treatments have failed (infusion of 1.5 mg/m² over a period of 24 hours every three weeks). Frequent side effects include infections, febrile eutropenia, vomiting, and hyperbilirubinemia. 1,895 patients with various soft tissue sarcomas were treated before approval in the framework of an "early access" program [61]. Efficacy is best for leiomyosarcomas, liposarcomas, and fibrosarcomas, but it is only moderate for AS: After three months, PFS was 25 % for AS versus 70 % for leiomyosarcomas, liposarcomas, and fibrosarcomas [62].

Pazopanib

Pazopanib is a (multi-) tyrosine kinase inhibitor with proven inhibition of receptors such as VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and PDGFR-β, fibroblast growth factor receptor-1 and -3, c-KIT, but it also inhibits other kinases such as B-RAF from the MAP kinase pathway. Approval covers selected subtypes of sarcoma *after* failure of chemotherapy in metastasized disease, including fibrosarcoma, myxofibrosarcoma, fibrohistiocytic sarcoma (pleomorphic malignant fibrous histiocytoma [MFH]), leiomyosarcoma, epithelioid hemangioendothelioma, and AS. The dosage is 800 mg per day orally. Frequent side effects include loss of appetite, taste disorders, headache, hypertension, diarrhea, vomiting, hair loss, and exanthemas.

The approval was based on the PALETTE study (Phase III, RCT, 372 patients [63]); PFS in the total cohort was significantly better with pazopanib (4.6 months) than with placebo (1.6 months). OS was not significantly improved. Among the few AS patients included in the treatment arm (n = 6), PFS was also prolonged to 3 months. More comprehensive data on pazopanib for malignant vascular tumors can be found in a retrospective EORTC study [64]: In 40 patients with advanced AS and ten with epithelioid hemangioendothelioma, 20 % of the cutaneous and non-cutaneous tumors as well as primary and radiation-induced sarcomas responded to treatment. Median PFS was three months (95 % confidence interval [CI] 2.1–4.4), median OS was 9.9 months (95 %-CI 6.5–11.3).

Other experimental medical approaches

The outlined data on palliation and prognosis with classical chemotherapy suggest a need for new concepts to improve the situation. All of the therapeutic approaches described below are attractive as concepts but have not so far been evaluated in a sufficient number of patients. They must therefore be considered experimental at this point in time.

Vascular targeting with anti-VEGF, bevacizumab, showed partial response in visceral and cutaneous AS. Agulnik et al. [65] reported 17 % PR and 50 % SD in 30 patients with visceral and cutaneous AS, with a mean latency of 26 weeks until disease progression.

There is also some limited experience on the efficacy of bevacizumab in combination with paclitaxel. After three treatment cycles in eleven patients with advanced and pre-treated cutaneous and visceral AS, Bui et al. [66] found one CR (9 %), four PR (36 %), two SD (18 %), and six PD (36 %).

Sorafenib, a multikinase inhibitor, has repeatedly shown a therapeutic effect for AS in individual case reports [67]. One series (n = 41) of the French Sarcoma Group (cutaneous and visceral AS) showed a limited response only in patients pre-treated with chemotherapy: median PFS 1.8 versus 3.8 months, OS was twelve versus nine months [68].

Anti-angiogenetic targeting in combination with metronomic chemotherapy and modern biomodulators may be an option. In one Phase II study, for example, patients with advanced and chemotherapy-refractory angiosarcoma received second-line treatment with an anti-angiogenetic triple combination consisting of 45 mg/d pioglitazone (PPARγ agonist), 25 mg/d rofecoxib (NSAID, Cox-II inhibitor), and metronomic trofosfamide (3 × 50 mg/d) orally as a daily long-term treatment, with encouraging results. Out of six patients with otherwise chemotherapy-refractory AS, two achieved CR, one PR, and three SD (PFS 7.7 months) with tolerable side effects (anemia, peripheral edemas) (Table 8) [69]. Additional administration

Table 8 Synopsis of the modalities of systemic treatments of angiosarcoma.

Drug/scheme	Dosage	Results	Notes [Reference]
Paclitaxel	80 mg/m² on day 1, 8, 15, for 4 weeks	30 patients PFS of 74 % after 2 mo. and 45 % after 4 mo.	ANGIOTAX study - [55]
Paclitaxel	Various treatment schemes (retrospective analysis)	32 patients RR of 62 %, (all AS), to 75 % (scalp)	EORTC study [59]
Paclitaxel	140 mg/m² i.v. continuously for 6 days every four weeks	3 PR, 2 CRs, 3 PD	[53]
Doxorubicin, peg. lip.	50 mg/m² d1 every four weeks	3 PR, 2 SD, 1 PD	
Gemcitabine	1000 mg/m² weekly in week 1–3, every four weeks	25 patients CR + PR were at 68 %	[60]
Trofosfamide Rofecoxib* Pioglitazon	3 × 50 mg orally per day continuous treatment 25 mg orally per day continuous treatment 45 mg orally per day continuous treatment	2 CR, 1 PR, 3 SD	Mainly second line after previous treatments with the abovementioned drugs, low toxicity, oral treatment on an outpatient basis [69]
Sorafenib	2 × 400 mg 9 months	Median PFS 1.8 resp. 3.8 months, OS was 12 resp. 9 months	Response only in patients pre-treated with chemotherapy [68]
Trabectedin, Ecteinascidin-743	1.5 mg/m² BS Infusion over 24 hours every three weeks	25 % PFS after 3 months in AS (moderate effect) vs. 70 % in leiomyosarcoma, liposarcoma, and fibrosarcoma (marked effect)	Second line can be used in advanced sarcomas [62]
Pazopanib	800 mg orally per day	Median PFS and OS three months (95 % CI 2.1–4.4) resp. 9.9 months (95 % CI 6.5–11.3) in advanced AS	Second line can be used in advanced sarcomas [64]

Abbr.: AS, Angiosarcoma; RR, response rate; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression-free survival; OS, overall survival, 95 % CI, 95 % confidence interval; BS, body surface.
*Rofecoxib was withdrawn from the market due to possible cardiac side effects after long-term treatment; it can be replaced by (for example) etoricoxib 60 mg/d.

of interferon α may improve the chances of response to the anti-angiogenetic treatments described above [70].

Propranolol is an established treatment option for hemangioma in infants. Individual positive case reports have been published with propranolol as a complementary medication in combination with other AS treatment; and there are also data from experimental models. However, it is too early to offer a general recommendation [71–73].

Role of electrochemotherapy

Guida M et al. (2016) [74] used electrochemotherapy (ECT) for treating 19 advanced angiosarcomas. The objective response rate was 12/19 (63 %), including eight cases of complete remission. The one-year local PFS rate (1JLPFS) of 68 % with this method indicates a potential for local tumor control in patients who have exhausted all other options for local treatment. Both pain control and bleeding control were convincing in about one-third of patients. In 2019, Zhou und Mei [75] published data from the so-called InspECT study (International Network for Sharing Practices in ECT), with comparable results: In 20 patients with very advanced AS, objective tumor response was observed in 80 %, half of the cases showed complete remission. Bleeding control was achieved in 13 out of 14 patients, average LPFS was 10.9 months.

Immunotherapeutic approaches and perspectives

Intralesional administration of rIL2 has led to complete remission in individual cases [76]. More comprehensive reports are available on the combination of these injections with radiotherapy [77–79]. Hata et al. [45] reported a local tumor control rate of 86 % after three years with application of X-rays/electrons of 50 Gy and a boost of 20 Gy over 35 fractions, with subsequent administration of rIL2 (17 patients). The definitive role of rIL2 has not been sufficiently assessed in studies, but the data suggest a role of the immune system in tumor control.

In this context, immune checkpoint inhibitors (ICI) have also recently been studied in small series and individual cases, based on the fact that AS are among the sarcomas with complex genetic damage. Significant rates of PD-1-expressing T-cell infiltrations were found in the tumors as well as PD-L1 expression in the tumor cells. In 106 cases, Honda et al. (2017), found 30 % positivity of PD-L1, as well as PD-1-positive infiltration in 17 %. Interestingly, this was associated with a tendency towards better prognosis [80]. In 2019, Florou et al. reported on a case series of seven patients. After twelve weeks of treatment with pembrolizumab, 5/7 of the patients showed an objective response, while 2/7 had progressed [81].

The potential role of ICI as a possible treatment option for AS cannot yet be conclusively assessed. Studies on the combination with experimental substances, such as AGEN1884, a CTLA-4 inhibitor (NCT02694822), are currently ongoing.

Table 9 Additional prognostic factors in cutaneous angiosarcomas [82].

Favorable features	Unfavorable features
Single tumor <5 cm	Multifocal, satellites, > 5cm
One region	Several regions
ECOG 0–1	ECOG 2–3, advanced age
Location on the trunk	Location head/neck, scalp
Superficial growth	Deep invasion, no solid portions
Solid portions	High Ki-67 expression
Inflammation	Necroses

10. Prognosis

AS usually has a poor prognosis. Small cases series have in the past reported five-year survival rates of only 12–24 %, with a median of about 18–28 months [2]. The smaller the series, the more can a "sampling effect" be assumed, so the historic numbers remain vague. A large and recent series with 434 cases of cutaneous AS by Albores-Saavedra et al. [82] (1973–2007, Mexico and USA) sheds new light on the prognosis of cutaneous AS: The average ten-year overall survival rate was 13.8 % in this cohort. As we might expect, the three-year survival rate was almost 0 % in patients with (mostly pulmonary) metastases, while in cases of regional metastases (lymph nodes) about 40 % of patents were still alive after three years and about 20 % after ten years. Of the patients with localized disease, 50 % were still alive after ten years. In view of these data, it would appear that the prognosis of cutaneous AS was, in the past, estimated to be worse than it actually is. With appropriate treatment, patients can certainly expect survival times of several years, depending on the initial conditions.

Table 9 shows additional criteria, which, in addition to the TNM stage, can be utilized for an individual prognosis:

– Solitary and superficial forms (tumor thickness is an important parameter!) with a diameter of less than 5 cm have, by their nature, a much more favorable prognosis than deeper, thicker, extensive, or multicentric tumors. Advanced age is

Table 10 Suggestions for follow-up examinations for cutaneous angiosarcoma.

Risk group	Year 1–3	Year 4–5	Year 6–10
Mainly favorable prognostic features According to section 10	Evaluation every 3 months: clinical examination, biopsy (if applicable), imaging (if applicable)	Evaluation every 6 months: clinical examination, biopsy (if applicable), imaging (if applicable)	Evaluation every 12 months: clinical examination, biopsy (if applicable), imaging (if applicable)
Mainly unfavorable prognostic features According to section 10	Evaluation every six weeks: clinical examination, biopsy (if applicable) In the first three years: additional ultrasound of the locoregional lymph nodes every 3 months and chest CT every 6 months	Evaluation every 3 months: clinical examination, biopsy (if applicable) Only in cases of clinical suspicion of progression beyond the primary location: Imaging (ultrasound, CT, MRI)	Evaluation every 6 months: clinical examination, biopsy (if applicable) Only in cases of clinical suspicion of progression beyond the primary location: Imaging (ultrasound, CT, MRI)

another factor that indicates shorter survival. Histopathologically, dense inflammatory infiltration is assumed to be a favorable factor for prognosis, while high Ki67 expression and necroses are categorized as unfavorable [83]. The same holds true for positive surgical margins [38].

- The prognosis for lymphedema-associated AS is probably somewhat worse than for other AS. Median survival times of only 19 versus 34 months have been reported. Metastases in the lungs, pleura, and thoracic wall are known causes of death [10, 19, 20].
- With little solid data, mammary AS would appear to have a particularly poor prognosis, with 90 % mortality within two years having been reported. The prognosis for radiation-induced mammary AS is similarly unfavorable. In 2012, Seinen reported on a series with a ten-year survival rate of 20 % despite primarily localized tumors amenable to R0 resection [8, 9].

11. Follow-up

Due to the rarity of angiosarcomas, valid data on the benefit of regular follow-up visits are not yet available. In most cases, individualized follow-up intervals of six weeks to three months are justified by the rapid progression and unfavorable prognosis. Imaging procedures should also be incorporated in the management plan as appropriate, taking into account the prognosis parameters, the TNM stage, and the typical sites of metastases.

The consented proposal of the guideline experts can be found in Table 10.

12. Rehabilitation and psychosocial care

Visible tumors on exposed areas of the body can cause significant distress for the patient. Psychosocial care and psycho-oncological counseling are always required in these cases, and in-patient rehabilitation may need to be considered.

Synopsis and references

A synopsis of the salient points of this guideline can be found in Table 11 in the online supplement. The reference list is also contained in the online supplement.

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