Angiosarcoma: a review of diagnosis and current treatment

Jun Cao1*, Jiale Wang2*, Chiyu He2, Meiyu Fang1

1Department of Comprehensive Medical Oncology, Key Laboratory of Head and Neck Cancer Translational Research of Zhejiang Province, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China; 2Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China. *Equal contributors.

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Abstract: 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.

Keywords: Angiosarcoma, aetiology, diagnosis, prognostic factors, chemotherapy, targeted therapy

Introduction

Angiosarcoma (AS) is a rare and highly aggressive malignant tumor, originating from lymphatic or vascular endothelial-cell [1]. It makes up less than 2% of all soft tissue sarcomas in humans and principally affects adult and elderly patients [1-3]. As a clinically and genetically heterogeneous subgroup of sarcomas, angiosarcoma can occur in any location of body [4]. The most common sites of angiosarcomas are cutaneous lesions (about 60% of cases), particularly the head and neck, and can also present within the soft tissues, visceral organs, bone and retroperitoneum [1, 4].

Angiosarcoma is an easily infiltrative tumor with high rate of local recurrence and metastasis [1, 5, 6]. The reported rates of advanced/metastatic disease at presentation vary from 16 to 44%, and the overall survival (OS) ranging from 6 to 16 months [7].

The pathogenesis of angiosarcoma has not been fully understood, definite risk factors include chronic lymphoedema, history of radiation, environmental carcinogens (vinyl chloride, thorium dioxide and arsenic) and several genetic syndromes [1, 2, 8]. According to epidemiology researches, angiosarcoma has a similar distribution between gender, and can occur at any ages. However cutaneous angiosarcoma has been found notably predilection for older male individuals, with a reported median age between 60 and 71 years [9].

The diagnosis of angiosarcoma remains a challenge. Due to its non-specificity of symptoms, it is difficult to discern angiosarcoma from other malignant neoplasms like anaplastic melanoma and epithelial carcinomas etc. [2, 10, 11]. The roles of ultrasound, computed tomography (CT) and magnetic resonance Imaging (MRI) in diagnosing angiosarcoma have their limitations [11]. Therefore, histological examination is significant for the diagnosis of angiosarcomas and immunohistochemical confirmation is required [6, 12]. Histologically, angiosarcoma is characterized by spindled, polygonal, epithelioid and primitive round cells, with expression both vascular and endothelial antigens on immunohisto-
Angiosarcoma: a review of diagnosis and current treatment

chemistry including Factor-VIII, CD31, CD34 and VEGF [1, 2, 10, 11].

Delayed diagnosis and the rarity of these tumors contribute to the difficulties in regarding best treatment and prognostic factors, radical surgery followed by adjuvant radiotherapy is thought the current optimal modality [2, 6, 10]. Regardless the controversy with respect to its side effect, conventional cytotoxic chemotherapy has been frequently used in treating inoperable and metastatic tumors [2, 4]. In addition, targeted medicines and immunotherapy have recently been studied as promising treatment for angiosarcomas [4, 13, 14].

Aetiology

While the pathogenesis is often unknown in majority of developing angiosarcoma cases, multiple aetiological factors, including radiation, chronic lymphoedema, environmental carcinogens and genetic syndromes, are established playing an important role in this disease.

Radiation

Radiation is a definite risk factor for the development of benign and malignant tumors. In retrospective studies, radiation has been associated with the heightened risk of tumors via radiation-induced gene mutation and concurrent chronic lymphoedema [15, 16]. According epidemiology survey, the common sources of radiation included patients receiving diagnostic and therapeutic radiation and occupational exposure [17].

Due to radiotherapy is a significant treatment in early stage sarcomas, particularly breast sarcomas, radiation-induced sarcomas is a main subtype of secondary sarcomas [18, 19]. In some reports, radiation-induced breast sarcomas have a long latency period after radiation, the median disease-free interval of which was 5-10 years [18, 20, 21]. Hence, a long-term follow-up, beyond the conventional 5-year oncological follow-up, is needed to achieve the prompt detection of recurrence [20].

The exact relationship between radiotherapy and angiosarcoma has not been fully confirmed, but several studies found, with the increased using of radiotherapy in the treatment of angiosarcoma and longer survival of tumor patients, the risk of radiation-induced angiosarcoma was increasing [22, 23]. There may also be a relationship between the high dose of radiotherapy and the incidence of angiosarcoma [24].

However, compared with the underlying benefit of radiotherapy, the overall risk of radiation-induced angiosarcoma is small and negligible.

Chronic lymphoedema

Chronic lymphoedema is another risk factor for angiosarcoma. The connection between long-standing chronic lymphoedema and angiosarcoma has been confirmed, called Stewart-Treves syndrome (STS) [25]. This disease typically presents in women after breast conservative surgery followed adjuvant radiotherapy. The adjuvant radiotherapy in treatment of early disease is thought to cause the development of STS [17, 25-27]. Parasitic infections such as filariasis or Milroy's disease, idiopathic, congenital, traumatic and filarial lymphoedema are also potential causes [28].

STS makes up approximately 5% of angiosarcomas, and often occurs 5-15 years after local treatment with surgery and radiotherapy [27]. The prognosis of STS is disappointing, with survival rate approximately of 10 months [26]. There is still controversy about the mechanism between some forms of chronic lymphedema and secondary angiosarcoma. In some cases, the mutation of a tumor genes, such as p53 and MYC, was thought to be a feasible cofactor [26, 29].

Environmental carcinogens

Although almost 75% of hepatic angiosarcomas don't have definite etiology [30]. Environmental carcinogens are the most common known factors for hepatic angiosarcoma, including vinyl chloride monomer and other industrial materials, iatrogenic exposure to colloidal thorium dioxide (thorotrast) for radiological examinations in the past, chronic arsenic ingestion and androgen [31, 32]. Most cases of this disease were caused by occupational exposure risks [33].

Genetic syndromes

About 3% of primary angiosarcomas are gene-induced, gene-associated diseases. Such as bilateral retinoblastoma, reiklingenhausen neurofibromatosis, ollier disease, maffucci disease,
xeroderma pigmentosa, and klippel-trenaunay syndrome etc. Familial syndromes are associated with angiosarcoma [34]. Some recent genome analysis showed that the dysregulation of angiogenic pathways was a significant part in aetiology of angiosarcomas and other tumor suppressor genes were found the association with angiosarcomas. Whereas the clinical significance of these findings still should be elucidated [6, 8].

**Epidemiology**

Angiosarcoma is a highly malignancy of endothelial tumor and accounts about 2-3% of all adult soft tissue sarcomas. This tumor can occur in any location of the body, but has a notably predilection for the skin and superficial soft tissue [8, 10]. The cutaneous angiosarcoma makes up two-thirds of all cases [10]. Due to its aggressive nature with the tendency to distant organ metastasize, the lung and brain are the most common sites of metastasize with a poor prognosis [1]. Previous studies reported that the 5-year survival rate of angiosarcoma patients was among 30-40% and the OS ranging from 6 to 16 months. Up to 20-40% of patients suffered from the local recurrence or metastasis [1, 10, 35]. According to the research, the distribution of angiosarcoma was tended to the older male individuals among 60-70 years old, especially in cutaneous angiosarcomas [36, 37].

**Diagnosis**

**Clinical presentation**

Diagnosing angiosarcoma remains a challenge due to the non-specificity of presentations. Common clinical presentations include abdominal discomfort, nausea, vomiting and altered bowel habits [6, 38]. Cutaneous angiosarcoma can present as single or multiple bluish or red nodules, and often ulcerate or bleed [8]. Hepatic angiosarcoma usually presents with right upper quadrant abdominal pain, jaundice and fatigue [31]. As the most common sites for metastases, lung and other visceral angiosarcoma may manifest as pleural disease, pleural effusion or dyspnea [21, 24].

**Diagnostic imaging**

Due to disease rarity and non-specificity clinical presentations, it is difficult to differentiate angiosarcomas from other malignant tumors [11]. Therefore, diagnostic imaging plays an important role in the initial diagnosis. Ultrasound, CT and MRI are common diagnostic tools of angiosarcoma.

Ultrasoundography is often used to identify effusion and lesions in visceral organs. Contrast enhanced ultrasound was reported as an excellent tool in diagnosis of hepatic angiosarcoma by Rauch et al. [39]. In cardiac angiosarcoma examination, transthoracic echocardiography has a high sensitivity in detecting tumors and is useful to explore the location, size, shape of tumors [40]. However, the limitation of ultrasoundography is that the large mass is ill-defined and not visualized on ultrasound image [41].

Compared with ultrasonography, CT and MRI could provide more additional information about tumors [11]. On CT, the common symapthies of lung angiosarcoma include pulmonary nodules, infiltrations, ground-glass opacity (GGO), etc. Cardiac angiosarcomas often show as a heterogeneous enhancing mass by CT [42]. Owing to histology characteristics of angiosarcoma, CT has its limitation in distinguishing some suspected tumor masses. MRI is superior to CT for differentiating between thrombus and tumor mass by providing detail information about the tissue characterization [11, 43, 44]. Whereas both CT and MRI carry a high sensitivity in discriminating angiosarcomas from other malignant tumors, immunohistochemical and pathological confirmation are required to reach a final diagnosis.

**Pathological examination**

Because most diagnostic imaging features are relatively non-specific, histological and Immunohistochemical examination are needed for definite diagnosis of angiosarcoma.

In clinical practice, there are mainly three ways to obtain histological specimen: 1. tumor resection and biopsy, followed by two surgeries after pathological diagnosis; 2. rapid pathological examination (frozen section), performed during tumor resection, and expanded resection was performed after diagnosis; 3. hollow needle puncture biopsy, performed before surgery, and surgical resection was performed after pathological diagnosis.
Histologically, the appearance of angiosarcoma varies widely and ranges from well-differentiated variants to poorly differentiated variants. In well-differentiated angiosarcoma, numerous irregular vascular channels lined by endothelial cells are demonstrated. Additionally, spindle-shaped, polygonal, epithelioid and primitive round cells, with increased mitotic activity and poorly formed vascular spaces, can be found in tissues of poorly differentiated angiosarcoma. Because of the heterogeneous cytoarchitectural features in poorly differentiated tumors, the histological identification of angiosarcoma is challenging [8, 45-47].

Immunohistochemical examination are often useful in the diagnosis of less-differentiated types of angiosarcomas. Angiosarcomas typically express endothelial markers including Factor-VIII-related antigen (Factor-VIIIRA), CD31, CD34 and vascular endothelial growth factor (VEGF). Among these markers, CD31 is the most common one found in more than half of the cases. With high sensitivity and specificity, CD31 is considered the gold standard of diagnosis in previous reports. At present, the expression of cytokeratin has been defined in epithelioid angiosarcomas, leading to confusion with poorly differentiated carcinomas [1, 6, 42, 46, 48].

**Gene alteration**

Cytogenetically, angiosarcoma is characterized by up-regulation of vascular-specific receptor tyrosine kinases, such as TIE1, KDR, TEK, and FLT1 [8, 49]. Although the genetic mutations of most primary angiosarcomas remain undefined. The angiogenesis genes have been confirmed to play key roles in secondary angiosarcomas, including MYC gene amplification, protein tyrosine phosphatase receptor type B (PTPRB) and phospholipase C gamma 1 mutation etc. [1, 50].

The proto-oncogene MYC is located at chromosome 8q24, the amplification of which have been reported as a prominent feature of secondary angiosarcomas [51, 52]. In some previous studies, MYC gene amplification was related to exposure to ultraviolet and sunlight and was found in more than 80% of radiation-induced angiosarcoma cases [51, 53]. Previous studies suggested that the amplification of MYC was only presented in secondary angiosarcomas and none of primary angiosarcomas cases showed MYC amplification or protein expression. Recently, in a small series of primary cutaneous angiosarcoma cases, MYC overexpression was present in 9 of 38 (24%) cases [54].

FLT4 gene maps to chromosome on 5q35, and encodes for VEGFR3 (Vascular endothelial growth factor receptor 3) which is thought to be involved in lymphatic differentiation [55]. FLT4 gene amplification is presented in approximately 25% of secondary angiosarcomas along with MYC amplification and causes the high FLT4 mRNA expression [56]. Based on this finding, targeting FLT4 is thought a potential therapeutic regimen for secondary angiosarcomas.

The rearrangements of CIC gene, a transcriptional repressor on chromosome 19q13.1, was reported in 9% (9/98) of patients with primary cutaneous angiosarcoma [53]. Additionally, the mutations of PTPRB and PLCG1, two angiogenesis-signaling gene, was reported as novel therapeutic targets in secondary angiosarcoma [57].

**Treatment**

Due to the rarity of these tumors and the lack of prospective evidence, the optimal management strategy is still argued. Current treatment options include surgery, radiotherapy and chemotherapy. The outcomes of treatment vary widely and are impacted by site, size, resectability and tumor type. In addition, targeted medicines and immunotherapy has been studied as promising treatment of angiosarcoma.

**Surgery**

Up to now, radical surgery remains the cornerstone of all treatments for angiosarcoma. Due to the extensive nature and the rapid progression of the disease, positive surgical margins are common in resection [1, 45]. In common, only very early and radical surgery with negative margins can offer the best prognosis to angiosarcoma [58, 59]. However, in the current study, the implications of surgical margin status on outcome of angiosarcoma remains unclear. In some studies, positive margins decreased OS and easily caused metastasis, but which was not demonstrated in other studies [1, 14, 60]. Despite this limitation, overall
negative surgical margins tend to improve patient survival and predict better outcome.

Additionally, because of intimate relationships with anatomical structures and metastatic nature of angiosarcoma, most patients with angiosarcomas of the head and neck are not suitable for surgical resection. Due to the difficulty achieving negative surgical margin, even after extensive surgery, the rate of local recurrence and distant metastasis are reported to be as high as 30-100% in these cases [1, 58, 60, 61].

To control the risk of local recurrence, adjuvant radiotherapy following surgery is often used in patients with negative microscopic margins or unresectable cases. Recently radical surgery with adjuvant radiotherapy has been shown improved outcome and survival rates.

**Radiotherapy**

While surgery is still thought to be the most reliable curative treatment for angiosarcoma, it is contraindicated in some older individuals and has a high rate of recurrence regardless of surgical margin status [1, 10]. For the past three decades, with the development of technologies, radiotherapy did show a tendency towards benefit in the treatment of angiosarcoma [45].

In spite of limited retrospective and prospective data, current reports supported that the radiation therapy is effective for inoperable patients with angiosarcoma and reduces the risk of postoperative recurrence [22, 24, 62].

Definitive radiotherapy has recently used in unresectable tumors such as angiosarcomas of the head and neck. Because there have been few previous studies on definitive radiotherapy for angiosarcomas, the optimal radiotherapy management is still unclear [1, 62]. According to a series of investigations, higher dose (>70 Gy) has been found may improve local control and OS when treating with radiotherapy alone [1, 62, 63].

However, no formal observation trials demonstrate whether radiation treatment alone is adequate for angiosarcomas, the adjuvant radiotherapy following radical surgery is confirmed the optimal combination for this disease [1, 62]. In some retrospective studies, the 5-years OS rates of combined therapy group are better than surgery alone group. Regardless of the limitations of data, these outcomes indicate that adjuvant radiotherapy following radical surgery is promising for improving OS of angiosarcomas.

In addition, factors influencing the efficacy of radiotherapy include details such as: treatment volume, treatment dose, radiation modality, and treatment technique. In large series of retrospective studies, large doses (>50 Gy) with wide fields are often recommended in controlling extensive angiosarcomas, and postoperative low-dose is effective in treating local disease following resection of tumor within 3 weeks [62, 64]. Due to the risk of radiation-induced angiosarcoma, further radiotherapy is cautiously utilized in treatment of tumors.

**Chemotherapy**

Due to the aggressive nature of angiosarcomas, about 50% of patients with localized disease will develop local recrudescence and distant metastases [1]. While there remain some controversies with respect to systemic chemotherapy for metastatic angiosarcoma, as well as little agreement on the choice of agents, general theory believe that adjuvant chemotherapy can bring limited benefits to patients after surgery or radiotherapy, and cytotoxic chemotherapy is the main treatment method for metastatic angiosarcoma [2].

In total, the primary chemotherapy agents included taxanes, doxorubicin, liposome doxorubicin and ifosfamide. In view of many angiosarcoma patients’ elderly age, the use of chemotherapy is limited by comorbidities and the risk of agents related toxicity [1, 2, 14].

**Anthracyclines:** In soft-tissue sarcomas, doxorubicin is the backbone of anthracyclines, providing a median OS of 8-14 months and the decreased rate of metastasis [65]. A recent pooled analysis of angiosarcoma patients from 11 prospective EORTC clinical trials of first-line anthracycline-based regimens showed that angiosarcomas have similar outcomes with first-line anthracycline-based regimens to other soft-tissue sarcomas, rather than poor prognosis [66].

Additionally, the combination of doxorubicin and ifosfamide was demonstrated with improved survivals of sarcomas compared to sin-
Angiosarcoma: a review of diagnosis and current treatment

gle-agent anthracycline [2]. Moreover, Ola-ratumab, a recombinant human immunoglobulin G subclass 1 (IgG1) monoclonal antibody, has been found improve both progression-free and OS in combination with doxorubicin for the first-line treatment of angiosarcomas [67]. However, owing to overlapping toxicity, these combinations had to be given with lower dose in treatment to avoid underlying complications, their potential should not be dismissed [65, 67].

In a randomized study, compared with traditional doxorubicin, liposome doxorubicin had the similar outcome of soft-tissue sarcomas treatment with favorable toxicity profile, less myelotoxicity but more skin toxicity [66]. Several small studies reported the similar conclusion [68]. Overall liposome doxorubicin was the optimal choice for angiosarcoma patients who cannot tolerate the toxicity of doxorubicin.

Taxanes: Clinically, paclitaxel is considered an active monotherapy for angiosarcomas and is often used in first or second line for metastatic disease. Larger retrospective studies have showed the effective of taxanes [2]. Fata et al. had first reported that 90% patients suffering from scalp angiosarcomas achieved a positive response with weekly paclitaxel, the median progression-free survival of which was 5 months [69]. Furthermore, according to the result of clinical trial for patients younger than 75 with advanced or metastatic angiosarcoma by Apice et al., the use of weekly paclitaxel seems to be an effective and well tolerated treatment, median OS was 18.6 months [70]. But the response rates of combination between weekly paclitaxel and other target agents for advanced angiosarcoma was disappointing in other Phase II Trials [71, 72].

While controversy still exists regarding the optimal selection and sequence of anthracycline and taxane-based chemotherapy, both anthracycline and taxane chemotherapy are still considered active and frequently recommended in treatment of angiosarcomas.

Targeted therapy

Vascular endothelial growth factor: Angiogenesis, or the formation of new capillary blood vessels, is an essential physiologic process for growth and development of human [73, 74]. In recent decades, proangiogenic growth factors and their receptors are found to play an important role in cancer control and progression, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) etc. [1, 2, 14, 75]. According to these significant findings, precise molecular pathogeneses for angiosarcoma is helpful to find new therapeutic targets for angiosarcomas.

VEGF is the most significant angiogenic factor, the overexpression of which is found in different subtypes of sarcomas including angiosarcoma [76, 77]. The previous experiments in animal model confirmed that high level expression of VEGF may resulted in fast-growing malignant tumors [78]. Furthermore, the therapeutic potential of VEGF and its receptor (VEGFR) for angiosarcoma was demonstrated in vitro [79].

Tyrosine kinase inhibitors (TKI) have been implemented in targeted therapy of angiosarcomas by inhibiting the VEGF/VEGFR signaling pathway, especially sorafenib and pazopanib [80]. In the description of phase II clinical trial by Penel et al., Sorafenib, a small molecule B-RAF and VEGFR inhibitor, was confirmed to be useful in treatment of angiosarcoma [81]. As another multi-targeted TKI, pazopanib, inhibiting VEGFR, PDGFR with significant suppressive activity, was found benefit in treatment of angiosarcomas [82, 83].

Although the disappointing responses to VEGF-targeted agents are reported in some angiosarcoma cases, the blockade of VEGF pathway is still a promising therapy for cancer patients and needs further research [84].

Adrenergic receptors: In retrospective studies of large patient cohorts, beta adrenergic receptor has been found express high levels in malignant vascular tumors involving angiosarcomas [85]. Amaya et al. reported that non-selective beta blocker, such as Propranolol, improved the outcomes of patients with metastatic angiosarcoma, median progression-free survival was extended to 9 months and median OS was 36 months [86]. In addition, the combination between bi-daily propranolol (40 mg) and weekly metronomic vinblastine (6 mg/m²) in a case series of 7 patients with angiosarcoma was reported 100% response rate and median progression-free of 11 months [87, 88].
**Immunotherapy**

Recently, the programmed death 1 (PD-1) and its receptors including ligand-1 (PD-L1) and ligand-2 (PD-L2) are thought to another effective therapeutic target for malignant tumors [89, 90]. According to a series of studies, using anti-PD-1 antibody in melanoma treatment showed encouraging survival outcomes of melanoma [91, 92]. Despite the lack of a large clinical trial, the curative effect of anti-PD-1 antibody for angiosarcoma was demonstrated in smaller trials [93]. Although there is no definitive evidence that angiosarcoma have similar outcomes with melanoma when using anti-PD-1 antibody, the potential for the use of these treatments is promising.

**Conclusion**

Angiosarcoma is a highly malignancy of endothelial tumor, with high rates of local and distant recurrence. Due to its pathological diversity, histological examination is the only reliable method for definite diagnosis of angiosarcomas. The majority of developing angiosarcoma cases have no clear etiology. Current treatments of angiosarcomas have their limitation. However, surgical resection with adjuvant radiotherapy remains the cornerstone of treatment for patients with localized angiosarcomas. It is challenging to avoid recurrence metastasis after treatment. Chemotherapy is the main treatment option for metastatic angiosarcoma despite it is hampered by the toxicities of frequently-used agents which are recommended in treatment. With the developing understanding of disease biology, biological therapies are the most potential field to find optimal treatment strategy for this rare disease. Targeted medicine is hopeful to improve the progression-free survival and OS and even achieve the complete cure of angiosarcoma. Overall further prospective studies are needed for better prevention, early diagnosis, and effective therapy.

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None.

**Address correspondence to:** Meiyu Fang, Department of Comprehensive Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, 1. Banshan East Road, Gongshu District, Hangzhou 310022, Zhejiang, China. E-mail: fangmy@zjcc.org.cn

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Angiosarcoma: a review of diagnosis and current treatment


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Angiosarcoma review of diagnosis and current treatment


Angiosarcoma: a review of diagnosis and current treatment


