Original Article

Prognostic usefulness of clinical features and pretreatment ^{18}F-FDG PET/CT metabolic parameters in patients with angiosarcoma

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Background: To investigate the prognostic value of clinical features and metabolic parameters in pretreatment ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/X-ray computed tomography (PET/CT) scans of patients with angiosarcoma, a rare neoplasm that has not been well characterized.

Methods: In this retrospective study, 19 patients with a histopathologically confirmed diagnosis of angiosarcoma who had undergone pretreatment ^{18}F-FDG PET/CT scans were enrolled. We recorded the age at presentation, sex, underlying diseases, sites of primary tumors, Karnofsky Performance Status (KPS) score, Eastern Cooperative Oncology Group (ECOG) score, time from onset to diagnosis, laboratory examinations, sites and sizes of primary tumors, treatment modalities, histologic features and American Joint Committee on Cancer (AJCC) stage, maximum standardized uptake value (SUVmax), average SUV (SUVavg), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of primary tumors and the whole body. Univariate and multivariate survival analyses for overall survival were performed according to the metabolic parameters and other clinical variables.

Results: Patients ranged in age from 27 to 79 years (median: 59 years) with different angiosarcoma types covering all tumor grades and subtypes. Seven (7/19) patients had anemia of varying degrees of severity. Lymph node metastases (n=10) and/or distant metastases (n=11) of angiosarcoma were common. Bone or bone marrow (10/19) and lung (8/19) were the most common distant metastatic organs. Patients with bone metastases, low hemoglobin levels and high ferritin levels had significantly poorer overall survival than those with non-bone metastases, normal hemoglobin levels and normal ferritin levels by the log-rank test, with P values of 0.027, 0.030 and 0.015, respectively. Patients with multiple organ metastases had significantly poorer overall survival than those with single organ metastasis (log-rank P=0.008). In multivariate survival analysis, only whole-body metabolic tumor volume using SUV_{max} cut-off value of 2.5 ($wMTV_{2.5}$) was a significant independent prognostic factor. For $wMTV_{2.5}$, 870.3 cm^3 was the best cut-off point to discriminate between a good and poor prognosis (log-rank P=0.01).

Conclusions: The systemic ^{18}F-FDG PET/CT with high sensitivity and specificity has significant

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advantages in the evaluation of angiosarcoma, particularly in detecting occult metastases. Bone metastases on ^{18}F-FDG PET/CT, low hemoglobin levels and high ferritin levels were all associated with a poorer prognosis. $MTV_{2.5}$ of the whole body is a significant independent metabolic prognostic factor for overall survival in patients with angiosarcoma.

Keywords: Angiosarcoma; fluoro-2-deoxy-D-glucose (FDG); positron emission tomography/X-ray computed tomography (PET/CT); clinical features; metabolic parameters; metabolic tumor volume; total lesion glycolysis (TLG); prognosis

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Introduction

Angiosarcoma is a highly malignant vascular tumor of endothelial cell origin constituting 1–2% of soft tissue sarcomas with a poor prognosis of a 24–34% 5-yr survival (1-9). These tumors can occur at any site in the body with great heterogeneity (10). Its pathogenesis is related to exposure to chemicals, radiation, chronic lymphedema, trauma and vasodilation (9,11). Integrated ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/X-ray computed tomography (PET/CT), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography are all diagnostic methods, but the final diagnosis requires pathology and immunohistochemistry. Because of the low incidence of angiosarcoma, scant evidence-based medicine data exist regarding morphological and functional imaging of these diseases.

Integrated ^{18}F-FDG PET/CT is the most widely used functional and metabolic imaging technique and provides more comprehensive and accurate information for clinicians presently (12,13). ^{18}F-FDG PET/CT has contributed to the detection of heterogeneous mesenchymal tumors of soft tissue or bone (14) and has great advantages in clinical grading, differentiation of benign and malignant tumors, clinical stage and restage, evaluation of local recurrence and monitoring of curative effects in sarcomas (15-18). Studies of ^{18}F-FDG PET/CT on angiosarcoma remain scarce because of the rarity of this tumor.

This retrospective study of 19 cases of pathologically diagnosed angiosarcoma before treatment explored the relationship among the clinical characteristics, laboratory examinations, ^{18}F-FDG PET/CT parameters and the prognosis of angiosarcoma.

We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-563/rc).

Methods

Patients

In 19 patients (10 women and 9 men) with histopathologically verified angiosarcoma, ^{18}F-FDG PET/CT was performed for the initial diagnosis before treatment between November 2014 and February 2020, and the outcome data were evaluated retrospectively.

Clinical characteristics and survival data were obtained from medical records and telephone call follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. IIT2020639A) and the requirement to obtain written informed consent was waived.

Patients who had any treatment for their tumor before ^{18}F-FDG PET/CT, had undergone ^{18}F-FDG PET/CT at another institution, or had incomplete clinical data were excluded from the study.

Patients ranged in age from 27 to 79 years (median age, 59 years) with different angiosarcoma types covering all tumor grades and subtypes. We recorded the age at presentation, sex, underlying diseases, sites of primary tumors, KPS, ECOG, time from onset to diagnosis, laboratory examinations, sites and sizes of primary tumors, treatment modalities, and outcome (survival) for each patient. The time from onset to diagnosis was defined as interval from the date when the patient reported chief complaint in admission records and the date of angiosarcoma diagnosis pathologically. Laboratory examinations included the white blood cell count, platelet

Table 1 Demographics and clinical characteristics of the patients

Characteristics	n (range or %)
Age, median (interquartile range), years	59 [27–79]
Sex, male/female	9/10 (47.4/52.6)
Underling diseases	
Hypertension	6 (31.6)
Local trauma history	1 (5.3)
Breast cancer and local radiotherapy	1 (5.3)
Hepatitis B cirrhosis	2 (10.5)
Family history	1 (5.3)
None	10 (52.6)
Sites of primary tumors	
Cutaneous	5 (26.4)
Right atrium	4 (21.0)
Liver	4 (21.0)
Bone	2 (10.5)
Artery (pulmonary artery/Iliac artery)	2 (10.5)
Spleen	1 (5.3)
Breast	1 (5.3)
Size of primary tumors, median (interquartile range), cm	5.7 (1.4–12.5)
Initial KPS, median [interquartile range]	80 [30–90]
Initial ECOG	
1/2/3/4	10 (52.6)/5 (26.4)/2 (10.5)/2 (10.5)
Time from onset to diagnosis, median [interquartile range], week	5 [1–60]
laboratory examination, median [interquartile range]	
White-cell count (10^9/L)	6.6 [2.4–15.2]
Platelet count (10^9/L)	250 [14–424]
Hemoglobin (g/dL)	110 [53–148]
C-reactive protein (mg/L)	17.9 [2.7–76.1]
Lactate dehydrogenase (U/L)	199 [148–709]
Ferritin (ng/mL)	351 [47.2–3,143.4]
Glutamic-pyruvic transaminase (U/L)	21 [14–515]
Creatinine (μmol/L)	68 [42–258]
Treatment modalities	
Surgery	6 (31.6)
Chemotherapy	6 (31.6)
Surgery+ chemotherapy	2 (10.5)
TACE (liver)*	2 (10.5)
None	3 (15.8)
Survival time, median (interquartile range), month	2.5 [1–24]

*, treatment by transcatheter arterial chemoembolization (TACE) in patients with primary hepatic angiosarcoma. KPS, Karnofsky Performance Status; ECOG, Eastern Cooperative Oncology Group.

count, hemoglobin (Hb) levels, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin (Fer) levels in serum, glutamic-pyruvic transaminase (GPT) and creatinine (Cr) (*Table 1*).

Histologic features and AJCC stage

All the patients had undergone biopsy of the tumor to establish the tumor grade and subtype (based on surgical specimens in 8 patients and biopsy specimens in 11 patients). The histologic features of the tumor were graded according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system (14) by an experienced sarcoma pathologist. The FNCLCC grade was determined by three parameters: differentiation, mitotic activity and extent of necrosis. Each parameter was scored as follows: differentiation [1–3], mitotic activity [1–3], and necrosis [0–2]. The scores were added to determine the grade. All the patients were assigned a clinical stage on ^{18}F-FDG PET/CT imaging using the seventh edition of the AJCC staging system (*Table 2*).

PET/CT imaging

All the patients were scanned on a dedicated PET/CT scanner (Biograph 16; Siemens, Germany). The patients had been fasting for at least 4–6 h and blood glucose levels were required to be less than 10 mmol/L before ^{18}F-FDG injection (3.75–5.55 MBq/kg). Scanning was started from the basal skull to mid-thigh after an uptake time of 40–60 min.

Table 2 Pathological characteristics and TNM staging of the patients

Characteristics	N (%)
Differentiation	
Grade 1	2 (10.5)
Grade 2	13 (68.4)
Grade 3	4 (20.1)
Mitotic activity	
Grade 1	3 (15.8)
Grade 2	14 (10.5)
Grade 3	2 (73.7)
Necrosis	
Grade 0	1 (5.3)
Grade 1	11 (57.9)
Grade 2	7 (36.8)
FNCLCC	
Grade 1	2 (10.5)
Grade 2	7 (36.8)
Grade 3	10 (52.6)
T classification	
T1	7 (36.8)
T2	3 (15.8)
T3	5 (26.3)
T4	4 (20.1)
N classification	
N0	9 (47.4)
N1	10 (52.6)
M classification	
M0	8 (42.1)
M1	11 (57.9)
Bone and marrow	10 (52.6)
Lung	8 (42.1)
Liver	2 (10.5)
Spleen	1 (5.3)
Single organ metastasis	3 (15.8)
Multiple organ metastasis	8 (42.1)
AJCC stage	
IB	1 (5.3)
II	3 (15.8)
IIIB	2 (10.5)
IV	13 (68.4)

FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; AJCC, American Joint Committee on Cancer.

Low-dose CT without intravenous or oral contrast scans were performed using a sixteen-slice helical CT with a continuous spiral technique (120 KeV; automatic current regulation adjusted to thickness and density of each patient's body; section thickness of 5 mm). PET scans were obtained for 3 min per frame and were reconstructed using iterative algorithm (Siemens). Additional scan of the extremities was acquired if the patient had tumors or suspected metastases on the lower extremities below the mid-thigh.

Measurements of the metabolic PET parameters

Experienced nuclear medicine physicians used volume viewer software on a dedicated workstation (MedEx), which provides automatic delineation of the region of interest (ROI) using an isocontour threshold method based on the SUV, to assess the initial diagnostic staging of ^{18}F-FDG PET/CT images. The metabolic tumor volume (MTV) was defined as the total tumor volume segmented via the threshold SUV. Two MTV segmentation methods were applied as an isocontour at an early SUV of 2.5 ($MTV_{2.5}$) or using fixed thresholds of 40% ($MTV_{40\%}$) of the maximum intratumoral ^{18}F-FDG activity. Total lesion glycolysis (TLG), another functional tumor parameter which determined the metabolic activity of tumors, was defined as a product of the SUV_{avg} multiplied by the MTV. Using two threshold SUVs, ten parameters were then measured and recorded: $pSUV_{max}$ (SUV_{max} of the primary lesion); $pSUV_{avg}$ (SUV_{avg} of the primary lesion); $pMTV_{40\%}$ ($MTV_{40\%}$ of the primary lesion); $pMTV_{2.5}$ ($MTV_{2.5}$ of the primary lesion); $pTLG_{40\%}$ ($TLG_{40\%}$ of the primary lesion); $pTLG_{2.5}$ ($TLG_{2.5}$ of the primary lesion); $wMTV_{40\%}$ ($MTV_{40\%}$ of whole body); $wMTV_{2.5}$ ($MTV_{2.5}$ of whole body); $wTLG_{40\%}$ ($TLG_{40\%}$ of whole body); $wTLG_{2.5}$ ($TLG_{2.5}$ of whole body) (*Table 3*).

Table 3 Metabolic parameters of ^{18}F-FDG PET/CT for patients with angiosarcoma

Characteristics	Median (interquartile range)
Primary tumor (n=19)	
SUV_{max}	6.8 (3.4–39.8)
SUV_{avg}	5.3 (1.5–24.1)
$MTV_{40\%}$	144.2 (9.7–876.9)
$TLG_{40\%}$	944.9 (39.8–5,049.5)
$MTV_{2.5}$	240.3 (13.3–3,072.3)
$TLG_{2.5}$	2,012.6 (16.5–17,756.9)
Metastatic tumor (n=13)	
$MT_{V40\%}$	285.5 (0*–2,786.5)
$TLG_{40\%}$	1,084.9 (0–8,283.3)
$MTV_{2.5}$	920.0 (0–5,711.4)
$TLG_{2.5}$	3,616.9 (0–19,418.74)
Whole body (n=19)	
$MTV_{40\%}$	315.6 (9.7–2,960.6)
$TLG_{40\%}$	2,714.2 (90.4–9,496.4)
$MTV_{2.5}$	870.3 (21.4–5,906.3)
$TLG_{2.5}$	5,070.6 (66.0–20,974.2)

*, FDG uptake of lung metastatic lesions was too low to measure MTV and TLG in one patient. ^{18}F-FDG, ^{18}F-2-fluoro-2-deoxy-D-glucose; PET/CT, positron emission tomography/X-ray computed tomography; SUV_{max}, maximum standardized uptake value; SUV_{avg}, average standardized uptake value; $MTV_{2.5}$, metabolic tumor volume using SUV_{max} cut-off value of 2.5; $MTV_{40\%}$, metabolic tumor volume using 40% of SUV_{max} as threshold; $TLG_{40\%}$, total lesion glycolysis using SUV_{max} cut-off value of 2.5; $TLG_{2.5}$, total lesion glycolysis using 40% of SUV_{max} as threshold.

Statistical analysis

All the statistical analyses were conducted using IBM SPSS Statistics software (version 20; SPSS Inc., Chicago, USA). Overall survival was measured from the date of initial diagnosis to death (18 patients) or the last follow-up (1 patient). The univariate analyses of the variables tested for survival included age, sex, underlying diseases, sites of primary tumors, KPS, ECOG, time from onset to diagnosis, laboratory examinations, sites and sizes of primary tumor, AJCC stage (T classification, N classification, M classification), pathological grading (differentiation, mitosis, necrosis and FNCLCC), metabolic metrics (SUV_{max} and SUV_{avg} of the primary tumor, the MTV and TLG of primary tumor and whole body), and treatment modalities. Univariate and multivariate Cox proportional hazards model, which yields hazard ratios (HR), were used to select potential predictors and assess the potential independent effect of the variables. Survival was analyzed by the Kaplan-Meier method. The log-rank method was used to identify optimal cut points for continuous variables.

Results

Clinical and laboratory characteristics

Four patients had secondary angiosarcoma, including one patient with a history of trauma at tumor sites, one patient with radiotherapy at tumor sites of breast cancer and two patients with hepatitis B cirrhosis. A female patient with primary angiosarcoma of right atrium had a family history of her mother having angiosarcoma of the breast. One-third of the patients (n=6) had a history of hypertension. Cutaneous angiosarcomas (26.3%, n=5) were the most common sites of primary tumors, including the head and neck (n=2), chest (n=1), upper arm (n=1) and abdominal wall (n=1). In 14 patients (73.7%), tumors had a visceral or deep soft tissue origin, including the right atrium (n=4), liver (n=4), bone (n=2), artery (n=2), spleen (n=1) and breast (n=1) (*Figure 1*). Two rare cases were located in the primary artery, one in the left pulmonary artery and the other in the left internal iliac artery (*Figure 2*). The median primary tumor length was 5.7 cm, with an interquartile range from 1.4 to 12.5 cm. The median KPS score was 80, with an interquartile range from 30 to 90. The KPS score is low in elderly patients. The ECOG performance status grade was 1 in 10 patients, 2 in 5 patients, 3 in 2 patients and 4 in 2 patients. The median time from the onset to diagnosis was 5 weeks, with an interquartile range from 1 to 60 weeks. The median and interquartile ranges of laboratory testing are summarized in *Table 1*.

The median (interquartile range) scores for the Hb levels were 110 (53–148 g/dL). Seven patients had anemia of varying degrees of severity (4 cases of mild anemia, 2 cases of moderate anemia and 1 case of severe anemia). CRP increased in nearly half of the patients (10/19), with a median (interquartile range) of 17.9 (2.7–76.1 mg/L). The median survival time was 2.5 months (interquartile range, 1–24 months).

Eighteen patients died from multiple organ failure because of primary tumor progression. Three patients

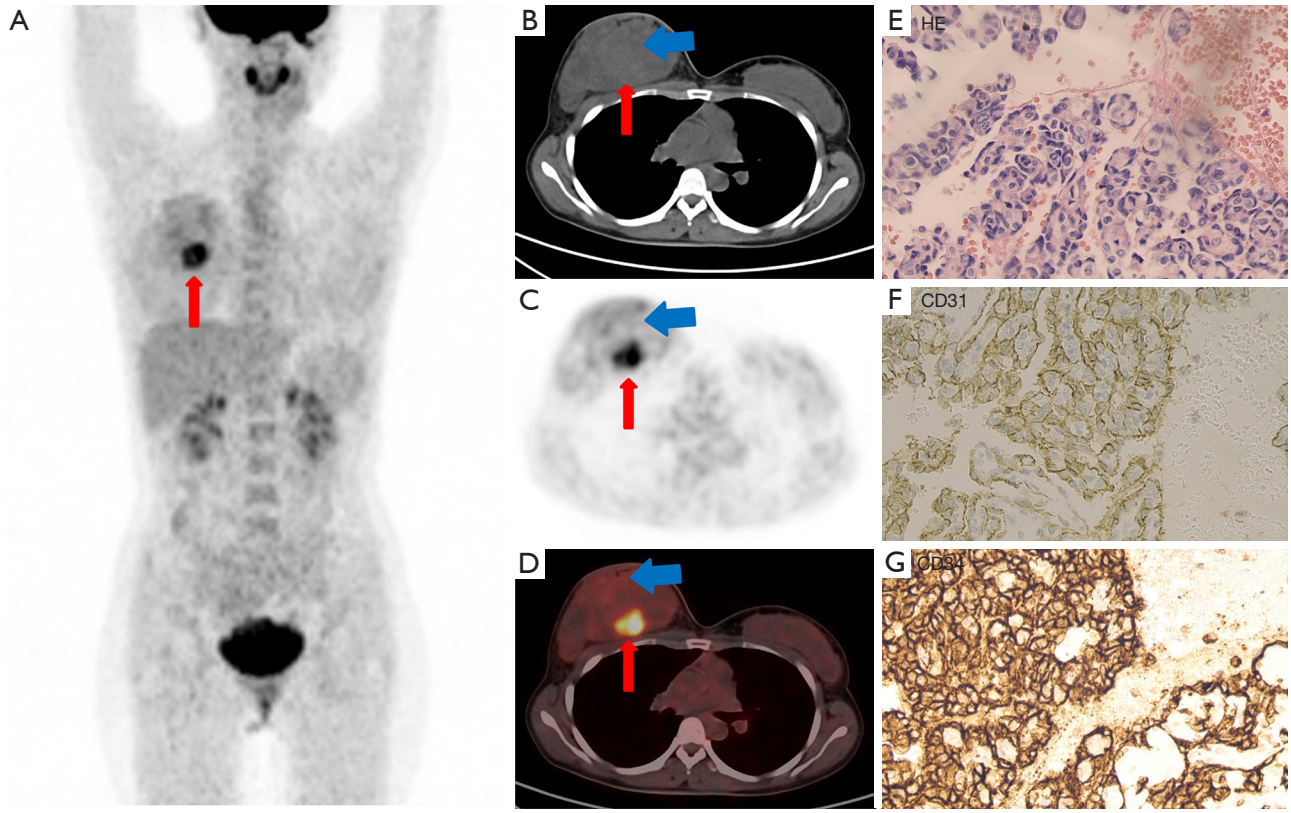

Figure 1 A 30-year-old woman with no tumor history presented with a growing mass in the right breast in the last year. Clinical and ultrasound examination presentations suggested a malignant neoplasm. ^{18}F-FDG PET/CT was performed, showing a hypermetabolic mass in the right breast on maximum intensity projection (A, red arrow). Axial slices (B-D) showed a 9.6*6.7 cm^2 heterogeneous mesenchymal tumor with high metabolism in central region with an SUV_{max} of 4.4 (B-D, red arrows) and mild metabolism in marginal regions with an SUV_{max} of 1.8 (B-D, blue arrows). Right breast resection and axillary lymph node dissection were performed by the surgeon. Hematoxylin-eosin staining (E, magnification, ×400) showed that the tumor tissue infiltrated growth was arranged in the vascular network with highly cellular atypia, obvious mitosis, extensive bleeding and necrosis. Immunohistochemistry presented tumor cell positivity for CD31 staining (F, magnification, ×400) and CD34 staining (G, magnification, ×400).

were treated only for vital support without surgery or chemotherapy because of unstable vital signs at the time of the diagnosis of angiosarcoma.

Histologic features and TNM stage

Histologic features and TNM stage are summarized in *Table 2*. Differentiation grade 2 (n=13), mitotic activity grade 2 (n=14) and necrosis grade 1 (n=11) were the most common histological parameter classifications, and FNCLCC grades 2–3 dominated in tumor histologic grading (17/19). Lymph node metastases (n=10) and/or distant metastases (n=11) of angiosarcoma were common. These patients were advanced with AJCC stage IV at the time of diagnosis. Distant metastases (n=11) included single organ metastasis (n=3) and multiple organ metastases (n=8). Bone or bone marrow (10/19) and lung (8/19) were the most common distant metastatic organs. Seven patients had metastases to bone (or bone marrow) and lung at the same time on ^{18}F-FDG PET/CT (*Figure 2A*). Bone metastases were characterized by osteolytic bone destruction with mild and moderate increases in FDG metabolism (SUV_{max} 1.4–8.2). Four cases of bone marrow metastases without obvious bone destruction were diagnosed by bone marrow biopsy of the right iliac bone because of anemia, including 2 patients with occult bone marrow hypermetabolism (*Figure 2B*,*2C*) and 2 patients with normal bone marrow metabolism on ^{18}F-FDG PET/CT. Additionally, 2 patients with bone

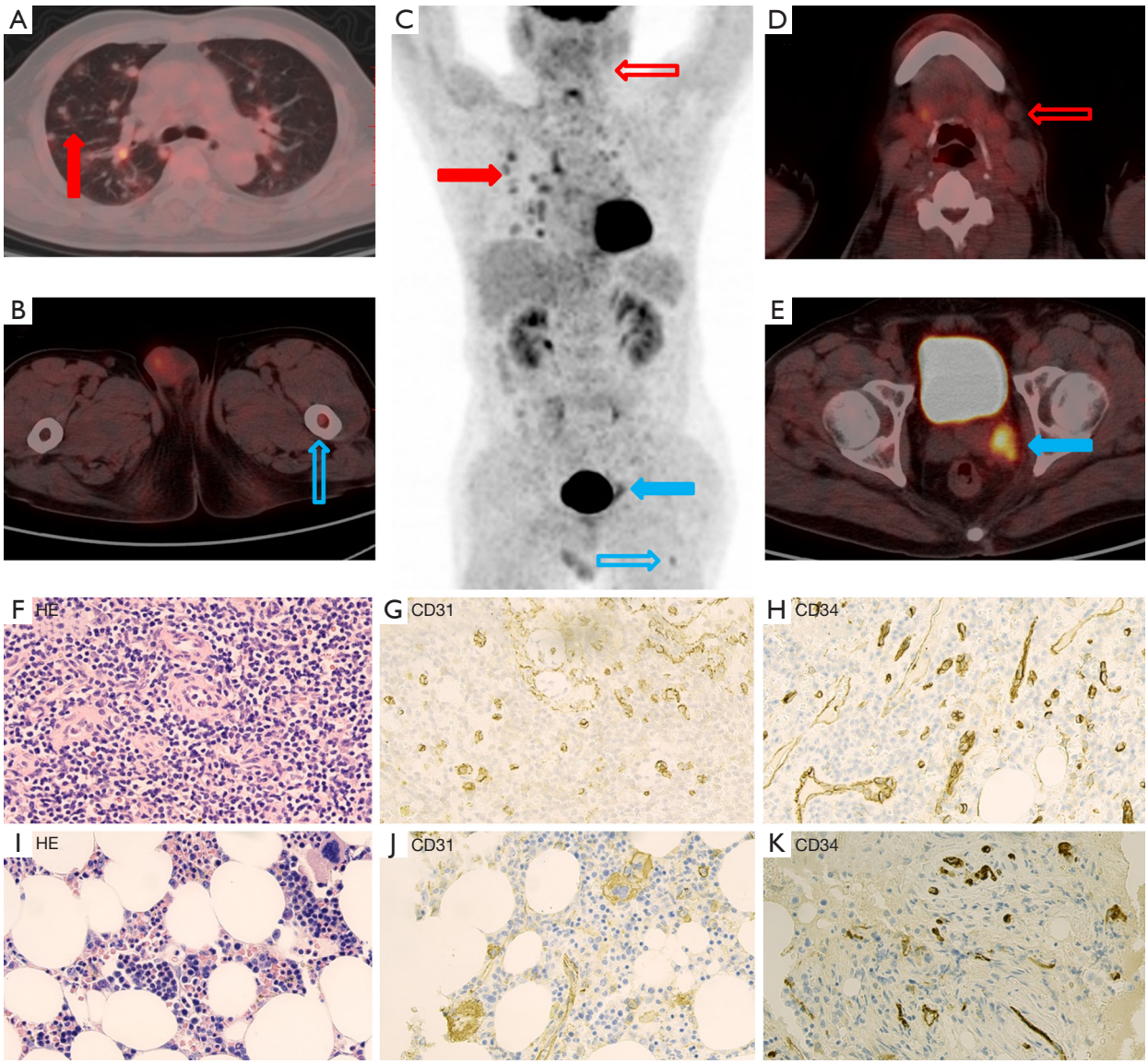

Figure 2 A 73-year-old male patient was admitted to the hospital for two months with recurrent cough and bloody sputum. Lung CT showed multiple pulmonary nodules, and malignant lung metastases were suspected. Further FDG PET/CT was performed to identify the primary tumor and stage this suspicious disease. The maximum intensity projection (C) and axial slice (A,B,D,E) images of the FDG PET/CT revealed multiple mild hypermetabolic solid and grinding glass nodules with an SUV_{max} of 4.2 in both lungs (A,C, red solid arrows) and a hypermetabolic mass with an SUV_{max} of 5.1 and a size of 1.3*1.4 cm^2 in the left pelvic cavity next to the seminal vesicle with a suspected origin of the left internal iliac vessels (A,E, blue solid arrows). This mass was associated with a slight increase in the FDG uptake with an SUV_{max} of 2.3 in the upper medullary cavity of the left femur (B,C, blue hollow arrows) and an FDG-negative lymph node approximately 1.2*1.3 cm^2 in size in the left mandibular lymph node (B,C, red hollow arrows). Pathological examination, immunohistochemistry of left lymph node resection (F-H) and bone marrow biopsy (I-K) both suggested angiosarcoma metastases. Hematoxylin-eosin staining (F,I, magnification, ×400) showed that the tumor cells were round, oval or fusiform, with obvious heterogeneity and arranged in cord-like or anastomotic vessels. Immunohistochemistry noted tumor cells positive for CD31 staining (G,J, magnification, ×400) and CD34 staining (H,K, magnification, ×400).

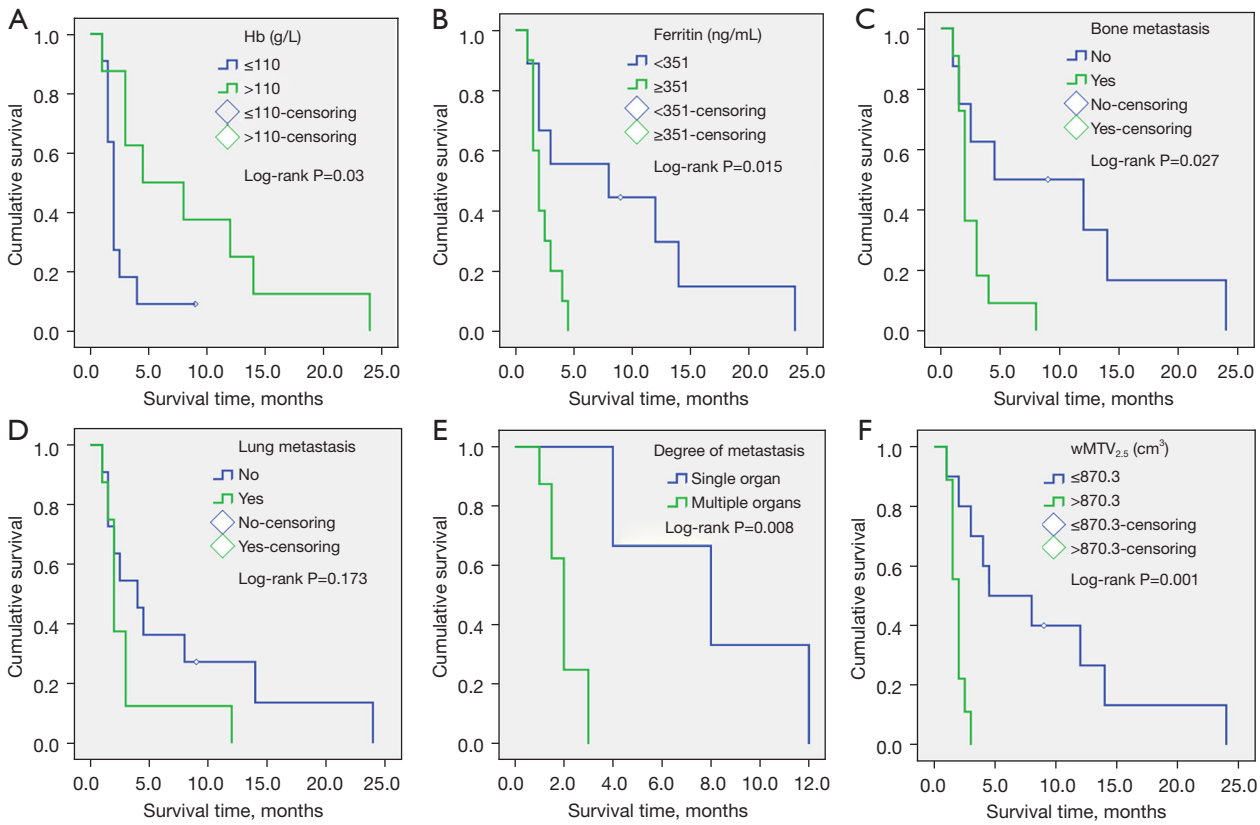

Figure 3 Kaplan-Meier overall survival curves for all the patients (n=19) (A-D,F). Kaplan-Meier overall survival curves for the distant metastases cohort (n=11) (E). (A) Kaplan-Meier curves for hemoglobin (Hb) of the whole cohort. A significant difference was observed between the two pacing sites, with a P value of 0.03 by the log-rank test. (B) Kaplan-Meier curves for ferritin (Fer) of the whole cohort. A significant difference was observed between the two pacing sites, with a P value of 0.015 by the log-rank test. (C) Kaplan-Meier curves for bone metastases of the whole cohort. A significant difference was observed between the two pacing sites, with a P value of 0.027 by the log-rank test. (D) Kaplan-Meier curves for lung metastases of the whole cohort. No significant difference was observed between the two pacing sites, with a P value of 0.173 by the log-rank test. (E) Kaplan-Meier curves for the metastatic degree of the distant metastases cohort. A significant difference was observed between the two pacing sites, with a P value of 0.008 by the log-rank test. (F) Kaplan-Meier survival curve of overall survival according to $wMTV_{2.5}$ (metabolic tumor volume of whole body using SUVmax cut-off value of 2.5) showed a cut-off of 870.3 cm^3 with a significant difference in survival (P=0.001).

marrow metastases showed myelofibrosis. Lung metastases were characterized by multiple margin blurred nodular and patchy shadows with mild FDG metabolism (SUV_{max} 0.4–4.7) on ^{18}F-FDG PET/CT and was often misdiagnosed as inflammation. Other false-negative lesions were also found in ^{18}F-FDG PET/CT such as left submandibular low ^{18}F-FDG uptake lymph nodes in a patient with advanced angiosarcoma (*Figure 2D*). The pathology showed metastases finally (*Figure 2F-2H*).

One patient with splenic angiosarcoma with AJCC stage I showed no signs of recurrence after radical surgery in the 9-month follow-up. Two patients had angiosarcoma with AJCC stage II (one case in the bone and the other in the right atrium) and AJCC stage IIIB (both in the liver with hepatitis B cirrhosis, misdiagnosed as hepatocellular carcinoma).

Survival analysis

Kaplan-Meier overall survival curves were constructed for all the patients (n=19). Data from Kaplan-Meier survival analysis for the low Hb level groups and normal Hb level groups (*Figure 3A*), high Fer level groups and normal Fer level groups (*Figure 3B*), bone metastases groups and non-

bone metastases groups (*Figure 3C*) and lung metastases groups and non-lung metastases groups (*Figure 3D*) are presented. Patients with bone metastases, low Hb levels and high Fer levels had significantly poorer overall survival than those with non-bone metastases, normal Hb and normal Fer groups by log-rank test, with P values of 0.027, 0.030 and 0.015, respectively. No significant difference was observed between the lung metastases groups and non-lung metastases groups (log-rank P=0.173). Patients with distant metastases (n=11) were divided into single organ metastasis group and multiple organ metastases group (*Figure 3E*). Patients with multiple metastases had significantly poorer overall survival than those with single metastasis (log-rank P=0.008). In the univariate survival analysis, KPS, Hb levels, bone metastases, $pTLG_{40\%}$ and $wMTV_{2.5}$ were significant predictors of overall survival (*Table 4*). Thus, high KPS, low Hb levels, bone metastases, high $pTLG_{40\%}$ and $wMTV_{2.5}$ were associated with worse outcomes. In multivariate survival analysis, only $wMTV_{2.5}$ was a significant independent prognostic factor (*Table 5*). For $wMTV_{2.5}$, 870.3 cm^3 was the best cut-off point to discriminate between a good and poor prognosis (log-rank P=0.001) (*Figure 3F*), with a high hazard ratio of 6.78 by univariate analysis using the Cox proportional hazards model (P=0.007).

Table 4 Results of univariate survival analyses by using Cox proportional hazard model

Variables (group)	HR	95% CI	P value
Age (1 year-increase)	0.990	0.970–1.020	0.690
Sex (male *vs*. female)	1.604	0.608–4.237	0.340
KPS (10 unit-increase)	0.967	0.936–0.999	0.044
ECOG PS (PS1 *vs*. PS2/3/4)	0.709	0.264–1.907	0.496
Time from onset to diagnose (1 month-increase)	0.975	0.042–1.008	0.131
White-cell count ($0.1*10^9$/L-increase)	0.996	0.845–1.174	0.962
Hemoglobin (0.1 g/dL-increase)	0.971	0.947–0.995	0.019
Platelet count ($1*10^9$/L-increase)	1.004	0.997–1.101	0.249
C-reactive protein (0.1 mg/L-increase)	1.019	0.996–1.042	0.100
Lactate dehydrogenase (1 U/L-increase)	1.002	0.999–1.005	0.292
Ferritin (1 U/L-increase)	1.000	1.000–1.001	0.109
Glutamic-pyruvic transaminase (1 U/L-increase)	1.002	0.997–1.006	0.416
Creatinine (1 U/L-increase)	1.003	0.993–1.014	0.523
Surgical therapy (yes *vs*. no)	1.620	0.575–4.560	0.361
Sites of primary tumors (cutaneous *vs*. deep)	0.440	0.134–1.452	0.178
Size of primary tumors (0.1 cm-increase)	0.869	0.735–1.028	0.101
Ki67 (10%-increase)	0.995	0.969–1.021	0.684
Differentiation (G3 *vs*. G1 and G2)	1.205	0.335–4.332	0.775
Mitotic activity (G1 *vs*. G2 and G3)	0.181	0.024–1.386	0.100
Necrosis (G2 *vs*. G0 and G1)	1.498	0.546–4.109	0.433
FNCLCC (G3 *vs*. G1 and G2)	1.465	0.524–4.100	0.567
T classification (T1 and T2 *vs*. T3 and T4)	2.942	0.886–9.775	0.078
N classification (N1 *vs*. N0)	1.737	0.549–5.078	0.313
M classification (M1 *vs*. M0)	0.890	0.328–2.421	0.820

Table 4 (*continued*)

Table 4 (*continued*)

Variables (group)	HR	95% CI	P value
Bone metastasis (yes *vs*. no)	0.295	0.089–0.098	0.047
Lung metastasis (yes *vs*. no)	0.522	0.191–1.430	0.206
AJCC stage (I and II *vs*. III and IV)	0.896	0.251–3.191	0.865
*$pSUV_{max}$ of (1-unit increase)	0.953	0.895–1.016	0.140
$pSUV_{avg}$ (1-unit increase)	0.861	0.732–1.012	0.069
$pMTV_{40\%}$ (1-unit increase)	1.000	0.997–1.002	0.762
$pMTV_{2.5}$ (1-unit increase)	1.000	1.000–1.001	0.590
$pTLG_{40\%}$ (1-cm^3 increase)	1.000	0.999–1.000	0.040
$pTLG_{2.5}$ (1-cm^3 increase)	1.000	1.000–1.000	0.286
#$wMTV_{40\%}$ (1-unit increase)	1.001	1.000–1.001	0.076
$wMTV_{2.5}$ (1-unit increase)	1.000	1.000–1.001	0.034
$wTLG_{40\%}$ (1-cm^3 increase)	1.000	1.000–1.000	0.595
$wTLG_{2.5}$ (1-cm^3 increase)	1.000	1.000–1.000	0.969

*, P indicates primary tumor; #, w indicates whole-body tumor. HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status; ECOG, Eastern Cooperative Oncology Group; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; AJCC, American Joint Committee on Cancer; SUV_{max}, maximum standardized uptake value; SUV_{avg}, average standardized uptake value; $MTV_{2.5}$, metabolic tumor volume using SUV_{max} cut-off value of 2.5; $MTV_{40\%}$, metabolic tumor volume using 40% of SUV_{max} as threshold; $TLG_{2.5}$, total lesion glycolysis using SUV_{max} cut-off value of 2.5; $TLG_{40\%}$, total lesion glycolysis using 40% of SUV_{max} as threshold.

Table 5 Results of multivariate analyses

Variables (group)	HR	95% CI	P value
KPS (10 unit-increase)	0.969	0.933–1.007	0.114
hemoglobin (0.1 g/dL-increase)	0.984	0.952–1.017	0.336
*$pTLG_{40\%}$ (1-cm^3 increase)	1.000	0.999–1.000	0.231
#$wMTV_{2.5}$ (1-unit increase)	1.001	1.000–1.001	0.035
Bone metastasis (yes *vs*. no)	0.746	0.336–4.061	1.220

*, P indicates primary tumor; #, w indicates whole-body tumor. HR, hazard ratio CI Confidence interval; KPS, Karnofsky Performance Status; $TLG_{40\%}$, total lesion glycolysis using 40% of SUV_{max} as threshold; $MTV_{2.5}$, metabolic tumor volume using SUV_{max} cut-off value of 2.5.

Discussion

The etiology and pathogenesis of angiosarcoma remain unclear. Approximately 3% of angiosarcoma cases are genetically induced (19). In our study, a female patient with primary angiosarcoma of the right atrium had a family history of her mother who having angiosarcoma of the breast. Some familial genetic factors may exist but have not been detected. Extrinsic risk factors include toxic substances (e.g., thorium oxide colloids, arsenic, and long-term use of anabolic steroids or estrogen) (20), medical history (e.g., chronic venous ulcers and Stewart-Treves syndrome), foreign bodies (e.g., vascular graft materials and surgical sponges) and ionizing radiation (in particular, radiation whose direct tumorigenic effects and ischemic changes resulting from long-term cellular repair can cause tissue damage) (21). Two patients with hepatitis B cirrhosis developed liver angiosarcoma rather than hepatocarcinoma in this study, suggesting that HBV infection is also an important risk factor for hepatic angiosarcoma.

Angiosarcoma has a poor prognosis. Previous literature

suggests that many factors leading to the prognosis of angiosarcoma patients include age, tumor size, metastasis, positive surgical margin, higher pathological tissue grade, deeper tumor site, physical status score and treatment pattern (19). A study of primary angiosarcoma of the heart in the United States showed that only 1/18 patient achieved R0 resection with a lower overall survival and indicated that the site of angiosarcoma was also a prognostic factor (22). In our prognostic evaluation, the patient's age, KPS, ECOG, tumor size, pathological grade, time of diagnosis, Ki67, treatment pattern and tumor location (deep and superficial, cardiac or non-cardiac) were not significant. The possible reasons for these results include three points: (I) the sample of 19 cases was too small; (II) angiosarcoma occurred in various regions and metastasized to distant areas easily; (III) pathological manifestations were varied. The rarity and clinical and pathological diversity of angiosarcoma make it difficult to study, diagnose and ultimately formulate appropriate treatment strategies. Systemic therapy, including radiotherapy, chemotherapy, targeted therapy and immunotherapy, is important to treat angiosarcoma, but no consensus exists on clinical treatment guidelines leading to differences in treatment.

However, there are no laboratory tests for early detection of angiosarcoma specifically and role of laboratory examination in assessing the prognosis of patients with angiosarcoma was unclear. Laboratory studies are usually unremarkable unless the mass effect causes the compression of critical organs and laboratory abnormalities or the disease is fairly advanced to cause subtle laboratory abnormalities (e.g., anemia of chronic disease and elevated sedimentation rate) (23). In our study, anemia was the most common laboratory abnormality, similar to other studies (2,22,23). Previous articles have not suggested a specific answer to this hypothesis. Possible explanations for anemia included anemia of chronic disease, bleeding, hemolysis, sequestration of erythroid elements, a tumor-associated factor or obliteration of the normal bone marrow hematopoietic elements. Surprisingly, we found significant fibrosis in bone marrow biopsies in 2 patients. Therefore, we speculated that bone marrow fibrosis caused by tumor metastasis to the bone marrow may be the main cause of anemia. We also found that half of the patients had a CRP increase, possibly due to secondary inflammation caused by tumor growth. However, few previous articles had assessed the prognosis of angiosarcoma using laboratory examination. Patients with bone metastases, low Hb levels and high Fer levels, which may represent existing internal causality, had a significantly poorer overall survival than those with non-bone metastases, normal Hb levels and normal Fer levels by the log-rank test in our study.

TNM staging of ^{18}F-FDG PET/CT did not predict the prognosis of angiosarcoma in our study. However, further analysis suggested that the prognosis of patients with multiple organ metastases was significantly worse than that of patients with single organ metastasis. ^{18}F-FDG PET/CT found some hidden metastases and performed more accurate TNM staging. Therefore, in clinical and ^{18}F-PET/CT evaluations of angiosarcoma, recommending using further grading of M stage with M1a (single organ metastasis) and M1b (multiple organ metastases) may be more accurate to assess the prognosis of patients. False-negative lesions were also found, such as left submandibular low ^{18}F-FDG uptake lymph nodes. Therefore, developing new tracers is urgent to improve the specificity and accuracy of imaging and the accuracy of prognosis judgment.

SUV_{max} is a useful indicator in the prognosis of patients with soft tissue sarcoma (22,24,25). However, SUV_{max} is a semiquantitative index and is influenced by biological and technological factors such as injection activity and scan duration (26). Therefore, multi-quantitative parameters and tumor description methods are necessary to predict the prognosis of angiosarcoma. Kato *et al*. (27) suggested that higher $PSUV_{max}$, MTV, whole-body TLG, primary TBR, and whole-body TLG ratio correlated significantly with a poorer overall survival in a study of 16 cases of angiosarcoma by ^{18}F-FDG PET/CT before treatment. In our study and multivariate survival analysis, only wMTV2.5 was shown to be a significant independent prognostic factor. The best cut-off point to discriminate between good and poor prognoses of $wMTV_{2.5}$ was 870.3 cm^3, which was significantly higher than the data (41.1 cm^3) suggested in a previous article by Kato (27). MTV and TLG have been well used as prognostic parameters in soft tissue sarcoma because they can reflect the load of tumors and biological behavior of tumors but have not yet obtained a more recognized grouping threshold. First, in our paper, the common fixed boundary value (at an early SUV of 2.5) was more meaningful in predicting the prognosis of angiosarcoma than the percentage boundary value (fixed thresholds of 40% of SUV_{max}), and we will continue to explore its optimal threshold in the following study. Second, MTV was more meaningful in predicting the prognosis of angiosarcoma than TLG. The reason may be that the MTV represents the tumor volume, likely indicating that the heterogeneity of the tumor increases and degree of

differentiation worsens with the growth of the tumor. TLG reflects tumor load. However, angiosarcoma and its metastatic lesions are often associated with necrosis and hand-drawn ROIs of SUV_{avg} measurement inhomogeneity. Therefore, TLG may not be as good as MTV in some negative or hypometabolic metastatic lesions. Finally, limited sample size was still the primary reason for our differences from previous studies. Knowledge of the interobserver variability of quantitative parameters is important in sarcomas because these tumors are frequently large and demonstrate heterogeneous ^{18}F-FDG uptake.

We recognized the following limitations of our study. First, the study was performed at a single-center and the sample size (n=19) was relatively small to achieve appropriate sampling of rare malignant neoplasms; multicenter analysis will be designed in a future study to achieve a better representation of angiosarcoma patient population. Second, we could not control for the effects of treatment modalities on OS. Therefore, effective and appropriate treatment strategies for angiosarcoma must be developed. Third, this was a retrospective study, and the use of ^{18}F-FDG PET/CT in the assessment of patients produced a potential bias toward an advanced tumor cohort.

Conclusions

Compared to the conventional imaging, the systemic ^{18}F-FDG PET/CT with high sensitivity and specificity has significant advantages in the evaluation of angiosarcoma, particularly in detecting occult metastases such as bone marrow, subcutaneous tissue, liver, and even hydrothorax and ascitic fluid. Furthermore, ^{18}F-FDG PET/CT with laboratory testing of Hb and Fer also play important roles in angiosarcoma. $MTV_{2.5}$ of the whole body is a significant independent metabolic prognostic factor for poor overall survival in patients with angiosarcoma.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-563/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-563/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. IIT2020639A) and the requirement to obtain written informed consent was waived.

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