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Characteristics and outcomes of primary pleural angiosarcoma

A retrospective study of 43 published cases

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Abstract

Primary pleural angiosarcoma (PPA) is an extremely rare malignancy for which there is no consensus on treatment. The clinical course of PPA is usually quickly fatal, regardless of the treatment used.

We summarized and evaluated a relatively large population of published PPA cases to assess prognostic factors, diagnostic approaches, treatment methods and clinical outcomes. Using the CNKI, Embase, and PubMed databases, literature published in English and Chinese from 1988 through 2020 was searched using the terms "primary pleural angiosarcoma," "pleural angiosarcoma," and "pleuropulmonary angiosarcoma."

A total of 43 patients with PPA were identified in retrospective case series and case reports. The median age at diagnosis was 64 years (range 24–87 years), and the median overall survival was 4 months (range 0.1–180 months). Approximately 80% of patients died from PPA within 10 months of diagnosis, and the 2-year survival rate was approximately 4.4%. In univariate analyses, the presence of pleural effusion and hemothorax were significant predictors of decreased survival, with hazard ratios (HRs) of 2.7 ($P = .04$) and 3.3 ($P = .006$), respectively. Sixteen patients received no therapy, and their prognosis was worse than patients who did receive therapy ($P = .019$). Radiation therapy improved survival more than no radiation therapy ($P = .007$). Patients appeared to derive clinical benefit from chemotherapy ($P = .048$). However, tumor resection did not seem to provide a survival benefit ($P = .051$). In multivariate analysis, tumor resection, and radiation were independent, statistically significant, positive predictors of better survival, with HRs of 0.3 ($P = .017$) and 0.1 ($P = .006$), respectively. The presence of hemothorax was an independent predictor of worse prognosis ($P = .006$).

Primary angiosarcoma of the pleura is a rare, poorly understood malignancy with a poor prognosis; hence, the clinical spectrum of PPA is not completely defined. By multivariate analysis, this retrospective study showed a survival benefit of tumor resection or radiation therapy, and the presence of hemothorax was a significant prognostic factor for poor outcomes.

Abbreviations: CI = confidence interval, HR = hazard ratio, PPA = primary pleural angiosarcoma.

Keywords: angiosarcoma, clinical, pleural angiosarcoma, prognosis, retrospective

1. Introduction

Angiosarcoma is a rare malignant tumor of endothelial origin that accounts for only 1% to 2% of all soft tissue sarcomas.[1,2] Tumors can occur in any part of the body, but the most common primary sites are cutaneous lesions (approximately 60% of cases), particularly in the head and neck; although, they can also present within the soft tissues, visceral organs, bone, and retroperitoneum.[2–4] There are major differences in the characteristics, behaviors, and prognosis of angiosarcoma among primary sites.[3] Primary pleural angiosarcoma (PPA), a highly malignant disease, is an extremely rare malignancy, and the literature is limited to case reports.[5–8] Delayed diagnosis and the rarity of these tumors contribute to difficulties in determining the best treatment and prognostic factors. With no consensus as to the most effective treatments, current treatment methods are guided by angiosarcoma studies and prior PPA cases. The treatments for PPA include surgical excision, radiotherapy and chemotherapy.[5–8] Nevertheless, the clinical course is usually aggressive and often becomes rapidly fatal, regardless of the treatment used.[7–9] Approximately 75% of patients die from PPA within 7 months, and all die within 24 months.[6]

PPA remains difficult to manage clinically due to the paucity of cases. For this study, we retrospectively summarized and evaluated 43 patients with PPA. To our knowledge, the study

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in this review represents the largest PPA cohort to date that identifies the clinical profiles, treatment outcomes, and prognostic factors associated with PPA. To achieve the study goals, the demographics and tumor characteristics of PPA patients at the time of diagnosis were summarized and evaluated in comparison with survival.

2. Methods

2.1. Data collection

We summarized and evaluated a relatively large population of recently published PPA cases to assess prognostic factors, diagnostic approaches, treatment methods, and clinical outcomes. Using the CNKI, Embase, and PubMed databases, literature published in English and Chinese from 1988 through 2020 was searched using the terms "primary pleural angiosarcoma," "pleural angiosarcoma," and "pleuropulmonary angiosarcoma." Cases were carefully reviewed, and published data were entered into a spreadsheet for inspection and analysis. Approval of the medical ethics committee was not required for this review because the case information was publicly available.

2.2. Statistical analysis

Survival was defined as the interval between date of PPA diagnosis and date of death or last follow-up. Survival was evaluated by Kaplan–Meier plots and Cox log-rank test. The Cox proportional hazards regression model was used to perform multivariate analyses and identify independent prognostic factors. P values $<.05$ were considered to indicate significant differences. The statistical software packages R (http://www.R-project.org, The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) were used to analyze all data.

3. Results

3.1. Patient characteristics and clinical presentation

Data from 43 PPA cases between 1988 and 2020 were included in the review. The median age at diagnosis was 64 years (range 24–87 years). The baseline characteristics of the patients are shown in Table 1. There was a male predominance (65% of cases). The ethnic distribution of these patients was 44% White, 5% Black, 49% Asian, and 2% other. Tuberculosis exposure was confirmed in 21% of patients. Tobacco smoking was reported in 28% and prior radiation therapy was reported in 9% of cases. Chronic expanding hematoma of the chest was considered a specific type of chronic empyema and was reported in 1 case. Only 1 patient (2%) was asymptomatic, and the most common presenting signs and symptoms were typical of pleural effusion, which occurred in 32 patients (74%). Symptoms were not restricted to dyspnea and included chest pain, hemoptysis, cough, fever, weight loss, fatigue and anorexia. Histopathological subtype data were provided for 43 patients and included 24 (56%) epithelioid angiosarcomas and 19 (44%) classical angiosarcomas. Fourty two cases had chest CT scan and/or MR image results, and positron emission computed tomography (PET-CT) data were present in 11 cases; in these cases, a chest mass was noted in 44% and pleural invasion was noted in 70% of cases, and invasion was circumferential in 26% and local in 44% of cases. Seventy four percent of patients had pleural effusion, but only 2% and 7% had pneumothorax and calcification, respectively. Nine percent of the patients were found to have bilateral multiple nodules, and the detection rates of single nodules or unilateral multiple nodules were 16% and 27%, respectively. A total of 47% of the patients were anemic, and 19% did not have anemia; 10 cases had

Table 1

Baseline characteristics of patients.

Characteristic	Number (%) or median (range)
Age (N = 43 cases)	64 (24–87)
Sex (N = 43 cases)	
Female	15 (35%)
Male	28 (65%)
Race/ethnicity (N = 43 cases)	
White	19 (44%)
Black	2 (5%)
Asian	21 (49%)
Unknown/other	1 (2%)
Exposure (N = 43 cases)	
Tobacco	12 (28%)
Tuberculosis	9 (21%)
Radiation	4 (9%)
Chronic expanding hematoma	1 (2%)
Histologic subtype (N = 43 cases)	
Epithelioid type	24 (56%)
Classical angiosarcomas	19 (44%)
Presenting signs and symptoms (N = 43 cases)	
No symptoms	1 (2%)
Dyspnea	23 (53%)
Chest pain	17 (40%)
Hemoptysis	12 (28%)
Cough	10 (23%)
Fever	4 (9%)
Weight loss	2 (5%)
Fatigue	2 (5%)
Anorexia	1 (2%)
Other symptoms	6 (14%)
Imaging findings of chest CT (N = 43 cases)	
Pneumothorax	1 (2%)
Mass	19 (44%)
Calcification	3 (7%)
Invasion of chest wall	2 (5%)
Pleural effusion	32 (74%)
Pleural invasion	30 (70%)
Pleural invasion (circumferential)	11 (26%)
Pleural invasion (local)	19 (44%)
Nodule	23 (53%)
Single nodule	7 (16%)
Unilateral multiple nodules	12 (27%)
Bilateral multiple nodules	4 (9%)
Anemia (N = 43 cases)	
Yes	20 (47%)
No	8 (19%)
Not mentioned	15 (35%)
Hemoglobin (g/L) (N = 10 cases)	71.5 (38.0–110.0)
Blood transfusion therapy (N = 43 cases)	8 (19%)
Metastases (N = 43 cases)	17 (40%)
Contralateral lung	7 (17%)
Contralateral pleura	3 (7%)
Skin	3 (7%)
Liver	3 (7%)
Brain	3 (7%)
Bone	7 (16%)
Soft tissue and other	7 (17%)

CT = computed tomography.

Table 2

Diagnostic methods, treatments, and clinical outcomes.

Characteristic	Number (%)
Diagnostic method (N = 43 cases)	
Thoracotomy biopsy or tumor resection	14 (33%)
Thoracoscopy	12 (28%)
Autopsy	4 (9%)
Percutaneous lung/pleural biopsy	7 (16%)
Other organ tumor resection	3 (7%)
Other organ puncture biopsy	2 (5%)
Skin biopsy	1 (2%)
Pleural effusion (N = 43 cases)	32 (74%)
Unilateral	23 (53%)
Bilateral	9 (21%)
Hemothorax	24 (56%)
Thoracentesis and drainage (N = 43 cases)	25 (58%)
Cytological examination (N = 43 cases)	16 (37%)
Bronchoscopy (N = 43 cases)	10 (23%)
Treatment (N = 42 cases)	
Tumor resection	12 (29%)
Chemotherapy	16 (38%)
Radiotherapy	7 (17%)
Surgical treatment of metastases	3 (7%)
Embolization treatment	2 (5%)
Pleurectomy	7 (17%)
Targeted therapy	4 (10%)
No treatment or palliative treatment	16 (38%)

hemoglobin values, and the median hemoglobin level was 71.5 g/L. Eight (19%) patients underwent blood transfusion. Metastasis occurred in 40%, and the sites of metastasis included but were not limited to the contralateral lung, liver, brain, and bone.

3.2. Diagnostic approach

In the present study, the median time until diagnosis (reported in 31 cases) was 1.4 months. Biopsy or tumor resection by thoracotomy were the most common diagnostic methods for PPA (n = 14, 33%) (Table 2). Diagnosis was made by thoracoscopy in 12 (28%) patients. Postmortem diagnosis was made in 4 (9%) cases. Sixteen cases underwent percutaneous lung/pleural biopsy; although, tumor tissue was successfully obtained in only 7 cases. Thoracentesis and drainage were performed in 25 patients; among them, the pleural effusion in 24 contained blood. Pleural cytology in 16 patients and bronchoscopy in 10 patients were performed but failed to obtain diagnostic material. The pathology of 6 cases was determined through metastasis.

3.3. Treatment and clinical outcomes

Treatment data are shown in Table 2. Sixteen patients never received any antitumor therapy, and their prognosis was worse than that of the treatment group (HR 2.6; 95% confidence interval (CI, 1.2–5.7; $P = .019$) (Fig. 1A and Table 3). Diagnosis was verified by postmortem investigations in 4 cases, and 3 cases without prognostic data were excluded from the prognostic outcome analysis. Radiation treatment was used in 7 patients (17%), and survival was better than that in patients who received no radiation treatment ($P = .007$) (Fig. 1B). Twenty nine percent of patients underwent tumor resection. However, surgery did not seem to provide a survival benefit ($P = .051$) (Fig. 1C). Pleurectomy also failed to provide a survival benefit (HR 0.4; 95% CI, 0.1–1.3; $P = .123$) (Table 3). Because of tumor metastasis, 2 patients underwent neurosurgery and 1 patient underwent intestinal surgery. Embolization therapy for the bronchial artery was performed to prevent further hemorrhage in two patients. Sixteen (38%) patients were treated with chemotherapy. Chemotherapy demonstrated significant benefits in terms of survival (median survival 7.8 months vs 1.4 months, HR 0.5; 95% CI, 0.2–1.0; $P = .048$) (Fig. 1D). Four patients were treated with targeted drugs: bevacizumab (2 cases), pazopanib (1 case), and sorafenib (1 case) with or without chemotherapy.

Approximately 80% of patients died from PPA within 10 months of diagnosis, and the 2-year survival rate was approximately 4.4% (Fig. 2). Univariate analysis was used to describe clinical characteristics by age, sex, tuberculosis, and radiation exposure, tobacco use, race, histologic subtype, pleural effusion, hemothorax, anemia, metastasis, and treatment (Table 3). The presence of pleural effusion and hemothorax were significant predictors of decreased survival, with HRs of 2.7 ($P = .04$) and 3.3 ($P = .006$), respectively (Fig. 1E-F).

In multivariate analysis, a Cox regression model was used to analyze the risk factors using the following possible prognostic factors: age, pleural effusion, hemothorax, metastasis, systemic chemotherapy, tumor resection, radiation, no therapy, and single-organ involvement in the chest. Thirty six cases (84%) had complete outcome data and were included in the analysis. Tumor resection and radiation were independent statistically significant positive predictors of better survival, with HRs of 0.3 ($P = .017$) and 0.1 ($P = .006$), respectively (Table 3). The presence of hemothorax demonstrated a trend toward worse outcomes (HR 3.4; 95% CI, 1.43–8.25; $P = .006$).

4. Discussion

PPA is an extremely rare malignancy. We performed a systematic literature search in CNKI, Embase and PubMed between 1988 and 2020 and retrospectively summarized 43 published cases with PPA to outline clinical features and to analyze outcomes. Given the rarity of PPA, its pathogenesis and etiology remain unclear and are still the object of much speculation. However, several exposure-related risk factors are known for this disease, including prior radiotherapy and a history of tuberculosis.[7,10–12] Likewise, tuberculosis exposure, radiation exposure and chronic expanding hematoma of the chest were reported in 14 (32%) cases in this study but did not correlate with outcome. Chronic inflammation and persistent physical stimulation are purported to result in PPA.[13–15]

The final diagnosis of PPA was based upon a histological study of the tumor samples. In the present series, the histologic subtype was epithelioid in 56% and classical in 44% of cases. This is inconsistent with the findings of previous reports that show that epithelioid variants account for 75% of PPA.[9,16] Univariate analysis of histologic subtype did not differ significantly with respect to overall survival in this case series. This is also incompatible with the results of a previous study that showed that histologic subtype correlated directly with malignant potential in patients with PPA.[17] Potential explanations include poor overall survival and a relatively small number of cases in this retrospective study. Intriguingly, metastases of PPA are not associated with a worse outcome, unlike other tumor types.[18,19] This difference may be explained by the fact that patients often die of recurring hemothorax and/or local progression within a short time.[9,20–22]

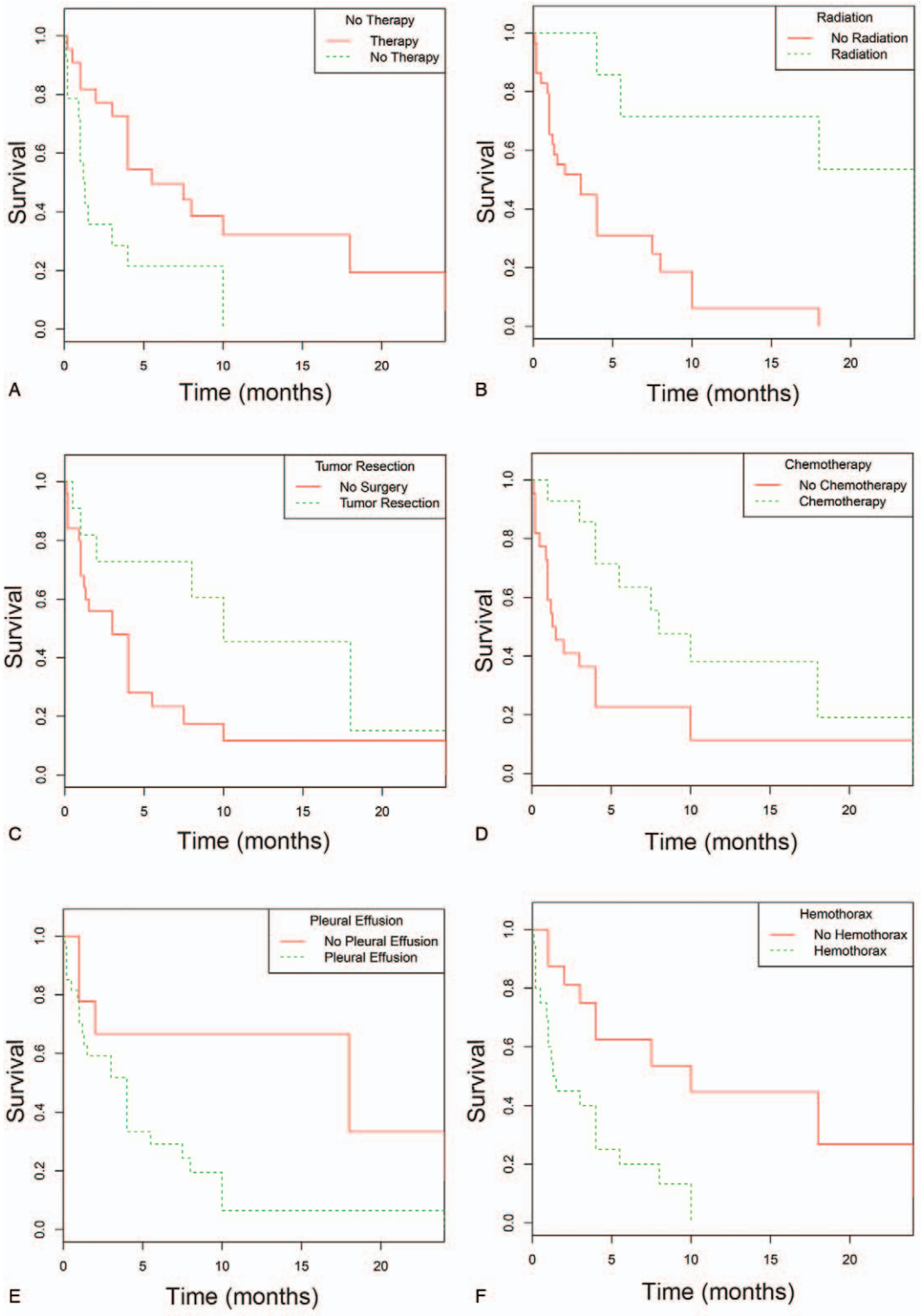

Figure 1. Kaplan–Meier curves for median overall survival: (A) No therapy vs therapy. Median survival time: 1.2 minutes vs 5.2 minutes, HR = 2.6, *P* = .019; (B) Radiation vs no radiation. Median survival time: 18 minutes vs 3.0 minutes, HR = 0.2, *P* = .007; (C) Tumor resection vs no surgery. Median survival time: 8.0 minutes vs 3.0 minutes, HR = 0.4, i = .051; (D) Chemotherapy vs no chemotherapy. Median survival time: 7.8 minutes vs 1.4 minutes, HR = 0.5, *P* = .048; (E) Pleural rffusion vs no pleural effusion. Median survival time: 4.0 minutes vs 7.0 minutes, HR = 2.7, *P* = .040; (F) hemothorax vs no hemothorax. Median survival time: 1.4 minutes vs 6.0 minutes, HR = 3.3, *P* = .006.

Table 3

Univariate and multivariate analysis of predictors affecting survival.

Univariate analysis (N = 36)			
Variable name	**Hazard ratio (HR)**	**95% CI for HR**	***P* value**
Sex	1.1	(0.5–2.4)	.715
Age (>65 vs <=65)	1.3	(0.6–2.6)	.51
Race (White vs non-White)	1	(0.5–2.0)	.911
Tobacco use (nonsmoker vs active/former)	1.4	(0.6–3.2)	.413
Tuberculosis and radiation exposure	1.1	(0.5–2.4)	.735
Histologic subtype	0.9	(0.4–1.9)	.783
Pleural effusion	2.7	(1.0–7.0)	.04*
Pleural effusion (bilateral vs others)	2.1	(0.9–4.7)	.084
Dyspnea	1.7	(0.8–3.5)	.178
Hemothorax	3.3	(1.4–7.8)	.006*
Anemia	0.5	(0.3–1.1)	.108
Metastases	1.4	(0.6–2.8)	.417
Number of metastatic sites (single vs multiple)	1.1	(0.5–2.3)	.9
Number of organ metastases (single vs multiple)	1.3	(0.6–2.9)	.526
Single-organ involvement in the chest	2.1	(0.7–5.7)	.166
Tumor resection	0.4	(0.2–1.0)	.051
Radiotherapy	0.2	(0.1–0.6)	.007*
Chemotherapy	0.5	(0.2–1.0)	.048*
Pleurectomy	0.4	(0.1–1.3)	.123
Targeted therapy	1.2	(0.3–3.9)	.803
No therapy or palliative treatment	2.6	(1.2–5.7)	.019*
Multivariate analysis (N = 36)			
Variable name	**Hazard ratio (HR)**	**95% CI for HR**	***P* value**
Hemothorax	3.4	(1.43–8.25)	.006*
Tumor resection	0.3	(0.12–0.81)	.017*
Radiotherapy	0.1	(0.04–0.57)	.006*

* $P < .05$ was considered significant. HR = hazard ratio, CI = confidence interval.

The clinical symptoms of PPA are not specific and are commonly represented by chest pain, dyspnea, hemoptysis, pleural effusion, and recurring hemothorax.[8,16,23,24] Radiology provides multiparametric morphological and important help for the diagnosis of PPA, but the radiological signs are also not very specific. PET-CT was used in 11 cases to estimate the stage and primary site. The diagnosis of PPA is strongly dependent on pathological findings. The median time until diagnosis was 1.4 months. Biopsy or tumor resection performed by thoracotomy or by video-assisted thoracoscopic surgery were by far the most frequently applied and helpful diagnostic tool for PPA, and they were applied in 26 (61%) cases.[25,26] Percutaneous lung/pleural biopsy was also supported by the present series.[16,27,28] Pleural fluid cytology yields a diagnosis in one-fourth of cases of pleural mesothelioma.[29] Unlike for pleural mesothelioma, pleural cytology had negative findings in all cases of PPA.[25]

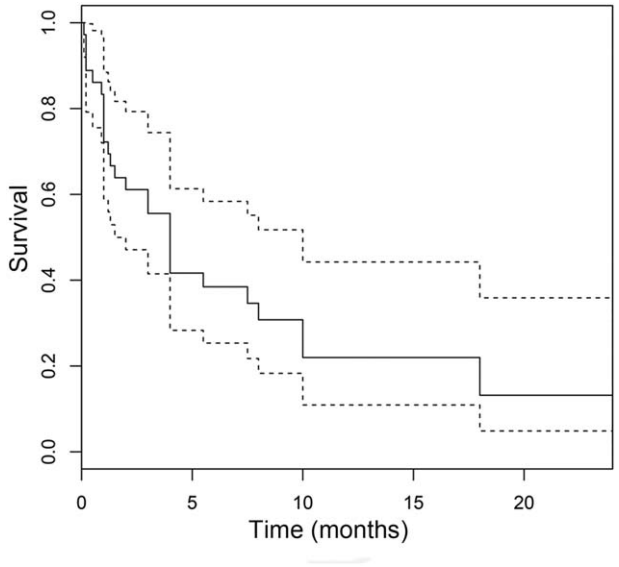

Figure 2. Survival times of 36 cases of pleural angiosarcoma. Approximately 80% of patients died within 10 months of diagnosis.

Treatment modalities for PPA include surgery, radiotherapy and/or chemotherapy, and surgery followed by adjuvant radiotherapy is considered the optimal current treatment modality. One patient with a large solitary angiosarcoma was successfully treated with surgery and postoperative radiotherapy, remaining well and asymptomatic after 15 years of follow-up.[8] Vascular embolization can be helpful in supporting hemostasis.[9,30] There are no consensus criteria for chemotherapy regimens for PPA; 16 (38%) patients received chemotherapy with or without targeted agents. Chemotherapy drugs included gemcitabine, docetaxel, paclitaxel, cisplatin, ifosfamide, doxorubicin, and/or albumin-bound paclitaxel.[31] Chemotherapy was associated with survival benefit in univariate analysis, which discordant results occurred in multivariate analysis. The role of chemotherapy may be limited, but radiotherapy can be effective in PPA. In addition, targeted medicines and immunotherapy have recently been studied as promising treatments for angiosarco-

mas.[32–35] Tyrosine kinase inhibitors (TKIs) have been implemented in targeted therapy of angiosarcomas, especially sorafenib and pazopanib.[32,34,35] In the present series, 4 patients were treated with targeted drugs: bevacizumab, pazopanib, and sorafenib.[36,37] Recently, a study described PD-L1 detection in 16/24 (66%) angiosarcoma samples.[38] One previous study reported a case of angiosarcoma of the nose treated with pembrolizumab, in which the patient received pembrolizumab for 13 cycles, which resulted in marked shrinkage of his liver disease and no new facial lesions.[39] Current treatment options for PPA are limited and poorly studied, making it necessary to consider treatment with tyrosine kinase inhibitors and checkpoint blockade therapies when appropriate. However, more studies are needed to establish the efficacy and safety of agents targeting the VEGF/VEGFR signaling pathway and immune checkpoint pathway in patients with PPA.

Although we represent the largest study to date on published PPA cases, our findings and conclusions should be interpreted with caution because of the relatively small number of cases and retrospective design of the study. The value of combined modality treatment was not assessed in this review due to few patients receiving combination therapy, which limits our ability for further analysis. Additionally, our characterization analysis of hemoglobin in patients with PPA was insufficient due to incomplete, limited data and a lack of corresponding information. Despite these limitations, we believe our analysis provides helpful information to physicians caring for individuals with PPA in clinical practice because the rarity of PPA makes it impossible to conduct prospective controlled trials or prospective cohort studies.

5. Conclusions

In summary, PPA remains an exceedingly rare and poorly defined malignancy. We report the first study of PPA that identified potentially useful clinical correlates for outcome. Specifically, tumor resection and radiation may be beneficial. The presence of hemothorax demonstrated a trend toward worse outcomes. Our findings provide important insight into this extremely rare and aggressive malignancy, and further study is needed to validate our findings and identify more accurate prognostic indicators of PPA.

Author contributions

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