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Review Article

Surgery Section

Diagnostic Challenges, Histopathological Insights, and Emerging Clinical Strategies in Primary Pleural Angiosarcoma: A Narrative Review

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ABSTRACT

The Primary Pleural Angiosarcoma (PPA) is a highly aggressive and rare endothelial cell malignancy of the pleura. The non-specific presenting features, coupled with its tendency to mimic mesothelioma, metastatic carcinomas, or benign pleural diseases, make its diagnosis particularly challenging. Delayed diagnosis, often till late in the course of the disease, and poor outcomes are common. The hallmark clinical presentations are haemorrhagic pleural effusion, chest pain, and progressive dyspnoea-all non-diagnostic. The present narrative review aimed to synthesise and critically evaluate the literature on PPA, focusing on diagnostic strategies, histopathological features, therapeutic modalities, and outcome patterns. From a qualitative analysis of published case reports and review articles published between 1988 and 2025, which were chosen for their extensive clinical, pathological, and Immunohistochemical (IHC) documentation pertinent to PPA, it is found that PPA arises almost exclusively in older men, characterised by rapidly progressive respiratory symptoms and a high frequency of haemothorax. Again, imaging studies are non-diagnostic, and cytology is of low sensitivity. The differential diagnosis is established by pleural biopsy, confirmed by IHC analysis with endothelial markers such as CD31, ERG, and FLI-1. Despite aggressive multimodal therapy comprising surgical resection, chemotherapy, and radiotherapy, median survival is woeful, less than six months from presentation in most series. In conclusion, PPA represents a frontier in both diagnosis and therapy within thoracic oncology. Early biopsy, accurate immunophenotyping, and multidisciplinary input are essential in maximising patient outcomes. Due to its rarity and dismal prognosis, more comprehensive and focused molecular studies are urgently needed to enhance diagnostic precision and therapeutic outcomes.

Keywords: Angiogenic markers, Biopsy accuracy, Endothelial phenotype, Haemothorax, Neoplasm progression, Thoracic oncology

INTRODUCTION

Primary Pleural Angiosarcoma (PPA) is an infrequent, aggressive vascular tumour originating from the endothelial lining of the pleura [1]. The extreme rarity, with fewer than 50 cases reported worldwide so far, leads to frequent diagnostic delays and a lack of uniformity in treatment approaches [2]. Limited experience among clinicians, pathologists, and radiologists leads to reliance on case reports and expert opinions for diagnosis and management, often resulting in late recognition and rapid clinical progression [3].

Epidemiology and Clinical Importance

Sarcomas are rare among malignant pleural tumours, with angiosarcoma accounting for approximately 1-2% of all soft-tissue sarcomas and representing only a small proportion of all malignant pleural tumours [4]. PPA primarily affects elderly males in the age group of 60-75 years and involves both visceral and parietal pleura. An aggressive course is characterised by pleural invasion and recurrent haemorrhagic effusions [5]. Diagnosis is challenging due to variable histology and nonspecific clinical features, and requires specialised IHC markers such as CD31, ERG, and FLI-1 [6]. Though asbestos exposure and irradiation of the chest have been considered as possible risk factors, no definite association with PPA has been established. Prognosis continues to be bad, with most patients dying within months of diagnosis [7]. The clinical relevance of PPA is its aggressive behaviour, diagnostic uncertainty, and poor survival; the majority of patients succumb within a few months after diagnosis [8].

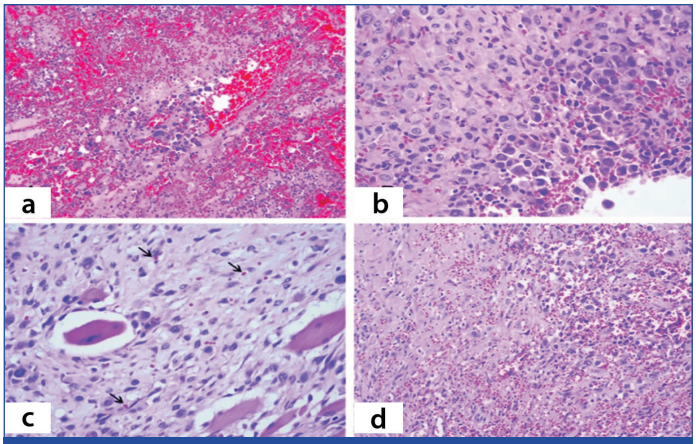
The PPA is notoriously difficult to diagnose early owing to the nonspecific clinical symptoms of chest pain, dyspnoea, cough, and weight loss it shares with more common pleural diseases, such as infections, mesothelioma, or metastatic cancer [9]. It often presents with haemorrhagic pleural effusion, although this is commonly misattributed to either trauma or inflammation. This overlap of symptoms results in misdiagnosis and delayed clinical suspicion, with multiple inconclusive thoracenteses leading to a delay in referral for definitive tissue biopsy [10].

Pathogenesis and Histologic Basis

These tumours arise from malignant transformation of vascular or lymphatic endothelial cells and can occur in any organ, including the skin, liver, and heart. In the pleura, they are thought to arise from the vascular component of the mesothelial layer [11]. Histologically, PPAs exhibit a varied architecture, comprising both epithelioid and spindle-shaped tumour cells [12]. Some neoplasms form well-developed vascular channels lined with atypical endothelial cells, while others comprise solid sheets of dysplastic cells. This variability often poses a challenge for histologic diagnosis because it mimics other pleural neoplasms [13]. Accordingly, definitive classification depends on IHC staining, an important test that confirms the vascular origin of these tumours and differentiates them from other malignancies, as demonstrated in [Table/Fig-1].

Clinical Presentation and Difficulty in Diagnosis

Patients with PPA usually present with nonspecific systemic symptoms such as chest pain, dyspnoea, cough, weight loss, and fatigue [14]. Haemorrhagic pleural effusion is a common finding but is often poorly attributed to the underlying disease. In cases of misdiagnosis, this has often been due to the overlap of symptoms



[Table/Fig-1]: a) Pleural angiosarcoma Showing scattered tumour cells in a haemorrhagic background; b) The solid sheets of epithelioid tumour cells may mimic mesothelioma or carcinoma; c) Intracytoplasmic lumina containing red blood cells (arrowhead) reflect endothelial differentiation; d) Anastomosing vascular spaces are typical for a vascular tumour (Haematoxylin-Eosin stain; magnification ×200 for a, d; ×400 for b, c).

with more common pleural diseases such as mesothelioma and metastatic carcinoma [15]. Available imaging modalities {X-ray, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography-Computed Tomography (PET-CT)} demonstrate nonspecific pleural changes, without definitive features indicative of PPA. Cytological examination of pleural fluid is often inconclusive due to tumour necrosis and low cell yield. Accurate diagnosis depends on meticulous histopathologic evaluation of biopsy specimens, best achieved by thoracoscopic techniques combined with immunohistochemistry [16].

Diagnostic Differentiation and Immunohistochemistry Role

The differential diagnosis includes mesothelioma, metastatic carcinomas, lymphoma, and solitary fibrous tumours, complicating clinical and pathological distinction [17]. Histologically, the PPA presents solid, vascular or papillary growth patterns with cellular atypia. Aberrant Cytokeratin (CK) expression in epithelioid variants requires comprehensive immunophenotyping. Molecular profiling is emerging, with techniques promising enhanced diagnostic and therapeutic precision [18].

Therapeutic Techniques and Outcomes

As PPA is so rare, there is no widely accepted treatment protocol. Surgery can only be attempted in very early and localised disease; it is rarely possible. Chemotherapy, usually with taxanes or anthracyclines, has a limited and short-lived effect. Radiotherapy plays a mainly palliative role. The immune checkpoint inhibitors targeting Programmed Cell Death Protein 1 (PD-1) are newer treatments that show promise but lack extensive clinical data in PPA. Despite various treatment combinations, the median survival remains low, typically ranging from three to six months following diagnosis [19,20].

REVIEW OF LITERATURE

Due to its rarity, the literature on PPA primarily consists of individual case reports and small series. Sedhai YR et al., described a landmark case and reviewed 46 others, with emphasis on histopathologic variability and the pitfalls of diagnosis [21]. Zhang S et al., described an epithelioid variant, emphasising the role of immunohistochemistry in distinguishing it from carcinoma [22]. Luan T et al., reviewed 11 cases of pulmonary angiosarcoma, with insight into treatment outcomes and clinical behaviour [23]. Machado I et al., described extensive histopathologic and IHC findings pertinent to differentiating angiosarcoma from other pleural neoplasms [24]. Kumari N et al., described cardiac angiosarcomas with comparative insight into systemic disease behaviour and treatments [25]. Bhaludin BN et al., described metastatic patterns and thoracic imaging features relevant to radiologic detection [26]. Collectively, these series form a basis for understanding PPA's clinical presentation, diagnostic markers, treatment limitations, and prognosis under controlled trials, as shown in [Table/Fig-2] [21-26].

MATERIALS AND METHODS

The present narrative literature search was conducted using electronic databases, including PubMed, Scopus, and Google Scholar, to identify relevant publications on PPA. The search was limited to English journals from 1988 to 2025. The search terms and Medical Subject Headings (MeSH) terms used were "PPA," "thoracic angiosarcoma," "vascular pleural tumour," and "pleural sarcoma." Manual screening of the reference lists of landmark papers was used to identify additional relevant studies.

Data Collection

Peer-reviewed papers that described clinical, histopathological, IHC, or therapeutic data for confirmed cases of PPA or closely related pulmonary angiosarcomas were included. Case reports, case series, and review articles were included in the analysis. Articles lacking comparative cardiac, cutaneous, or hepatic without pleural significance were excluded.

Data Extraction

From all the selected articles, relevant information was obtained, including patient demographics, clinical presentation, imaging findings, diagnostic methods, histological appearance, IHC markers, treatment techniques, and patient outcomes. All the studies were critically evaluated for methodological sufficiency, diagnostic accuracy, and applicability in the pleural context.

Study	Key findings	Research focus	Challenges/limitations	Future scope
Sedhai YR et al., (2020) [21]	Reviewed 46 PPA cases; stressed diagnostic complexity and clinical aggression	Case report + literature review	Isolated data; no unified protocol	Build diagnostic standards; pooled data review
Zhang S et al., (2015) [22]	Reported epithelioid PPA; stressed need for Immunohistochemical (IHC) confirmation	Subtype characterisation characterisation	Single case; mimics carcinoma	Explore diagnostic markers for PPA variants
Luan T et al., (2024) [23]	Analysed 11 pulmonary cases, including treatment responses and survival analysis	Clinical behaviour and management	Limited sample; no molecular profiling	Study immunotherapy, develop treatment algorithms
Machado I et al., (2021) [24]	Broad IHC review of angiosarcomas, including vascular markers relevant to pleural type	Histopathology and molecular differentiation	Non-site-specific; grouped soft-tissue sarcomas	Tailor IHC panels for pleural diagnosis
Kumari N et al., (2023) [25]	Reviewed cardiac angiosarcomas; insights into systemic angiosarcoma management	Behaviour of systemic angiosarcoma	Different origin; indirect relevance	Compare pleural and cardiac subtypes
Bhaludin BN et al., (2021) [26]	Highlighted thoracic imaging and metastasis trends in angiosarcomas	Radiological pattern recognition	Few pleural-specific findings	Design early radiologic protocols for pleural sarcomas

[Table/Fig-2]: Literature review – previous work on Primary Pleural Angiosarcoma (PPA) [21-26].

Synthesising Information

Qualitatively synthesised extracted data were used to highlight trends in diagnosis, histopathological characteristics, treatment approaches, and prognosis. The findings were thematically categorised and presented to highlight clinical challenges and new evidence.

RESULTS

Clinical Demographics and Symptomatology of Primary Pleural Angiosarcoma (PPA)

The PPA is most frequently found in elderly subjects, and most reported cases are found in patients aged 60-75 years. The reason for the slight male predominance reported in the literature is currently unknown. Unlike established environmental risk factors for mesothelioma, such as asbestos, PPA has no definable etiologic associations; however, a prior history of chest irradiation and chronic inflammatory disease has been reported in some series [27].

Clinically, PPA is associated with nonspecific thoracic symptoms; therefore, diagnosis is often delayed. Frequent symptoms reported are pleuritic chest pain and progressive dyspnoea, and these are frequently misdiagnosed as an infectious or inflammatory pleural syndrome [28]. Haemorrhagic pleural effusion is a characteristic but underdiagnosed feature, and often, there are serial thoracenteses before reaching a diagnosis. Other features are cough, weakness, and occasionally weight loss [29]. In a few cases, patients present in an advanced stage with respiratory failure or massive pleural effusions requiring urgent therapy. The course of the disease is usually aggressive. Pleural invasion, brisk tumour growth, and recurrent effusions are the norm [30]. Tumour growth into adjacent lung parenchyma or chest wall has been reported in some cases, further complicating the clinical picture. Due to the vascular nature of the tumour, spontaneous haemothorax and intrapleural bleeding can occur, with resultant life-threatening complications [31].

The nonspecific and overlapping presentation, which is more common in pleural disease, makes clinical suspicion of PPA challenging in the absence of histological evidence. Recognition of the pattern of acute symptom onset and haemorrhagic effusion can prompt earlier diagnostic intervention and increase clinical awareness, as shown in [Table/Fig-3] [27-31].

Radiologic Appearance and Imaging Diagnostic Challenges

Radiologic evaluation is critical in diagnosing suspected pleural cancers, such as PPA. Imaging in PPA is very nonspecific and often mimics more common processes, such as malignant mesothelioma or metastatic pleural disease. This simulation is a significant hindrance to early diagnosis [32].

The CT scan most commonly reveals irregular pleural thickening, nodular masses, or effusion, with or without pulmonary or chest wall invasion. Haemorrhagic pleural effusion typically occurs but is radiologically indistinguishable from effusions of inflammatory or infectious origin [33]. Patterns of enhancement on Contrast-Enhanced CT suggest hypervascularity but are not diagnostic of angiosarcoma. MRI has been applied in a few instances to assess soft-tissue extension and better delineate tumour margins. MRI can demonstrate heterogeneous signal intensities secondary to haemorrhage and necrosis, features of vascular tumours. It is rarely helpful in making a definitive diagnosis [34]. PET-CT has been Utilised to assess metabolic activity and identify metastatic lesions. Typically, it exhibits intense Fluorodeoxyglucose (FDG) uptake; however, this is observed across a wide range of malignancies and inflammatory processes, making it less specific [35,36].

In summary, imaging modalities are helpful for staging and procedural planning, but they are insufficient to differentiate PPA from other pleural malignancies. The absence of pathognomonic radiologic findings underscores the importance of tissue sampling and histopathologic diagnosis. Imaging should thus be employed to direct rather than supplant definitive diagnostic methods in suspected PPA, as shown in [Table/Fig-4] [32-36].

Cytology, Biopsy, and Diagnostic Limitations of Pleural Fluid Analysis

The diagnostic significance of pleural fluid cytology in PPA is minimal, which prevents early diagnosis. While pleural effusion, frequently haemorrhagic, is a frequent presenting sign, cytology is generally not helpful in giving definite proof of malignancy. This limitation results in abundant tumour necrosis, a low cellular yield in effusion samples, and morphologic features similar to those of benign reactive mesothelial cells or other tumours [37].

In most cases of PPA reported in the literature, diagnosis is significantly delayed as multiple thoracenteses often show inconclusive results. This was highlighted by Boucher LD et al., who described the cytologic features of angiosarcoma in fine-needle aspiration biopsies and pleural fluid specimens. Because cellularity and cytomorphology are highly variable, diagnosing angiosarcoma can be challenging. Even when malignant epithelioid cells are identified, their morphological features closely resemble those of metastatic carcinoma or mesothelioma, often leading to misdiagnosis because of the absence of unequivocal vascular differentiation on cytology [38]. Metovic J et al., emphasised that while immunocytochemistry is a valuable method for diagnosing pulmonary tumours, its effectiveness is often limited by the quality of the cellular material [39]. Miettinen M et al., further complicated the diagnosis when they reported that ERG, while a good endothelial marker may be a diagnostic pitfall for epithelioid sarcoma and should therefore be interpreted cautiously within a wide IHC panel. If any reasonable doubt exists about the endothelial nature of the tumour confirmation using a panel of endothelial markers, such as

Study	Demographics and risk factors	Clinical presentation	Symptoms and diagnostic challenges	Disease course and complications	Importance of early diagnosis	Study design
Yavuz H et al., (2023) [27]	Middle-aged male; spontaneous haemothorax	Acute chest pain, haemothorax	Haemorrhagic effusion misdiagnosed as trauma	Rapid deterioration and high mortality	Requires clinical suspicion for pleural bleeding	Case report
Bu C et al., (2024) [28]	PAA is mostly incidental; congenital and acquired risk factors	Often asymptomatic; detected via imaging	Non-specific; often confused with PH or aneurysm	Risk of rupture; massive haemoptysis	CTPA is essential for early detection	Review article
Szczyrek M et al., (2023) [29]	General pleural neoplasms; no PPA-specific risk factors	Symptoms vary with tumour type	MRI is underutilised for pleural diagnosis	Delayed detection leads to poor outcomes	MRI can improve early differentiation	Literature review
Chambergo-Michilot D et al., (2023) [30]	Cardiac AS: young patients; male predominance	Dyspnoea, effusion, and chest pain are common	Often diagnosed late due to vague symptoms	High-grade tumours; common metastasis	A multimodal strategy is needed for early identification	Systematic review
Li Z et al., (SEER-based) (2022) [31]	SEER analysis; more males; age 40-60	Variable: dyspnoea and cough are prominent	Diagnosis is limited by database coding	Short survival; poor prognosis	Registry data aids awareness	Retrospective database analysis

[Table/Fig-3]: Demographics and clinical features of PPA [27-31].
CTPA- Computed tomography pulmonary angiography; PH: Pulmonary hypertension

Author et al.,	Imaging modalities for PPA	Non-specific radiologic features	CT and MRI findings	Limitations and need for histopathology
Chong AR et al., (2024) [32]	CT, thoracoscopy	Pleural effusion, haemothorax	Right pleural mass with haemorrhagic effusion	Diagnosis confirmed only after thoracoscopic biopsy
Basiri R et al., (2024) [33]	CT, bronchoscopy	Pleural thickening, pyopneumothorax	Right hilar mass, effusion, collapse	Histopathology via thoracotomy is essential due to misleading imaging
Joyce A et al., (2025) [34]	CT, punch biopsy	Pericardial effusion	Mass in the right atrium	Tissue confirmation is required due to ambiguous imaging features
Thomas K et al., (2025) [35]	Various fluids + imaging	Variable cavity wall thickening	Radiology shows nonspecific fluid collections	Cytology alone is insufficient; it needs IHC and prior diagnosis
Janowski M et al., (2025) [36]	Whole body CT	A small bowel mass was found incidentally	Unusual lesion in a trauma setting	Histology is pivotal; imaging did not indicate a vascular neoplasm

[Table/Fig-4]: Radiologic features of Primary Pleural Angiosarcoma (PPA) [32-36].

CD31, CD34, and factor VIII-related antigen, should be performed to minimise misdiagnosis [40]. Despite these hurdles, an accurate histologic evaluation, supported by clinical and radiologic findings, remains paramount for improving diagnostic yield in PPA.

Given such limitations, the gold standard for diagnosis remains tissue biopsy. Image-guided core needle biopsies can present early histological information. Still, on most occasions, Video-Assisted Thoracoscopic Surgery (VATS) must provide sufficient material to facilitate appropriate histopathological and IHC analysis. A thoracoscopic biopsy enables direct endoscopic guidance and specific sampling of pleural masses, significantly improving the diagnostic yield [41].

The infrequency of PPA makes interpretation challenging, as pathologists typically do not consider angiosarcoma in the differential diagnosis at presentation. Thus, multidisciplinary communication between the thoracic surgeons, radiologists, and pathologists is necessary [42]. Lastly, while initial analysis of pleural fluid is performed, tissue-based assessment is essential for a definitive diagnosis, with biopsy playing a crucial role in suspected PPA [43].

Histopathological Patterns and Immunohistochemical (IHC) Profile

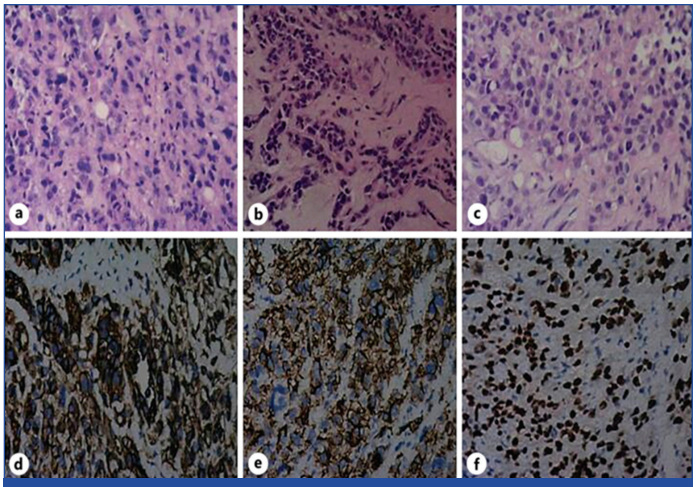
PPA is a very heterogeneous tumour histopathologically, hence difficult to diagnose without IHC support. The tumour can present in a spindle cell, epithelioid morphology, or a combination [44]. The spindle cell variant consists of elongated cells arranged in fascicles or in a storiform pattern. In contrast, the epithelioid variety consists of large, polygonal cells with nucleolated nuclei, abundant cytoplasm, and numerous mitotic figures [45]. Both patterns are characterised by necrosis and haemorrhage, reflecting the tumour's vascular nature, as shown in [Table/Fig-5] . Anastomosing blood channels lined with abnormal endothelial cells are a typical histological feature. However, this is absent in the poorly differentiated areas, and morphological diagnosis should not be relied upon. In such cases, IHC is employed [46].

The PPA will always express endothelial markers, such as CD31, ERG, and FLI-1, which are crucial for vascular lineage commitment. CD31 is the most sensitive and specific, and ERG and FLI-1 are also helpful markers. CD34 may also be positive, but its accuracy is lower, especially for ruling out other soft-tissue sarcomas. Epithelioid subtypes of PPA may also exhibit aberrant Cytokeratin (CK) expression and may be misdiagnosed as carcinoma or mesothelioma unless endothelial markers are tested simultaneously [47].

Because of this overlapping immune profile, a panel-based IHC strategy is necessary to prevent misdiagnosis. Combining morphology with restricted marker expression permits accurate classification and dictates management. Recognition of these histologic and IHC subtleties is essential for early and accurate diagnosis as shown in [Table/Fig-5] [48].

Treatment Modalities and Response Patterns

Treatment of PPA remains extremely challenging since the disease is sporadic and highly malignant, and there are no established treatment



[Table/Fig-5]: a-f) HE staining and immunohistochemistry (×200): Tumour cells in the pleura (a) are more heterogeneous than those in the chest wall (b) and lung tissue (c). Pleural immunohistochemistry (×200): CD31 (+) (d), CD34 (+) (e), and ERG (+) (f).

protocols. Treatment is often borrowed from angiosarcomas found elsewhere in the body, depending on the disease stage, the patient's performance status, and institutional preference [49].

The use of several multimodal approaches, comprising surgery, chemotherapy, and radiotherapy, has been highlighted by Yavuz H et al., Chambergo-Michilot D et al., and Li Z et al., [27,30,31]. However, no standardised protocols exist for their implementation. Surgical resection is typically considered for localised disease, while chemotherapy regimens often include taxanes and anthracyclines, providing modest benefits [27,30,31].

Surgical resection can be considered in localised disease. However, such a presentation is uncommon due to the tumour's aggressive nature and its propensity to present with diffuse pleural disease. Where possible, tumour resection provides symptomatic palliation but does not significantly affect long-term survival due to early recurrence and micrometastatic dissemination [50]. Chemotherapy is the mainstay of treatment, with taxane-based chemotherapy, such as paclitaxel and anthracycline-based chemotherapy, such as doxorubicin, providing limited improvement. These agents can transiently stabilise the disease but are rarely curative. Tumour resistance and patient decline during therapy limit treatment response [51]. Side-effects also preclude the completion of planned regimens, particularly in comorbid elderly patients. Radiotherapy has been employed as an adjuvant or palliative modality, particularly for the management of localised symptoms such as bleeding or chest wall invasion [52]. Its role, however, remains limited due to the radioresistance of sarcomas and the thoracic anatomic complexity. Novel therapies such as immune checkpoint inhibitors like PD-1 blockers have shown activity in soft-tissue angiosarcomas but lack evidence in PPA. Their potential utility awaits large case series and biomarker-guided trials [53].

Overall, the treatment outcome remains poor, with a median survival of less than six months, underscoring the urgent need for new therapies, as depicted in [Table/Fig-6] [49-53].

Study	Surgical management	Chemotherapy regimens	Radiotherapy applications	Emerging therapies	Treatment outcomes and challenges
Kao YC et al., (2011) [49]	VATS biopsy performed; definitive diagnosis achieved	Not administered due to poor condition	Not applied	None employed	Death within weeks due to rapid progression
Yu M et al., (2021) [50]	Lung biopsy via bronchoscopy is not diagnostic; surgery is avoided	No chemo was given due to poor clinical state	Not indicated	None	Fatal alveolar haemorrhage; delayed diagnosis
Piechuta A et al., (2016) [51]	VATS enabled diagnosis; no curative surgery was performed	Chemotherapy not discussed	Not explored in treatment	None discussed	Mortality within 3 months of presentation
Modrzewska K et al., (2015) [52]	Video-assisted thoracoscopic biopsy confirmed diagnosis; deteriorated	Treatment unsuccessful; specifics not mentioned	Not utilised	Not mentioned	Death post-biopsy due to haemorrhage
Abdelbaki A et al., (2018) [53]	No surgery; managed conservatively with supportive care	Not used due to late-stage disease	Not considered due to the vascular nature of the lesion	None available at diagnosis	Fatal course due to diagnostic ambiguity

[Table/Fig-6]: Treatment approaches for Primary Pleural Angiosarcoma (PPA) [49-53].

DISCUSSION

The PPA remains an elusive clinical entity because of its rarity, very aggressive biological behaviour, and lack of established diagnostic or therapeutic guidelines. Due to improved diagnostic techniques and oncologic treatments, the overall prognosis for patients with PPA has not been substantially enhanced over the last few decades [54]. This review compiles current evidence from case reports and series to provide the most pertinent information on the clinical presentation, diagnostic challenges, histopathological nuances, treatment options, and prognostic outlook of this highly aggressive vascular neoplasm.

The results of the present narrative review are consistent with several highly relevant published studies that emphasise the persistent diagnostic challenge and poor outcomes in PPA. Sedhai YR et al., revealed characteristic delays in diagnosis and aggressive clinical behaviour; most patients present with nonspecific symptoms and advanced disease at presentation, reflected in the uniformly poor survival rates [21]. Zhang S et al., reiterated the diagnostic pitfalls, particularly for the epithelioid variant, and the need for early, integrated assessment [22]. Luan T et al., contributed clinical series data comparing treatment responses and survival, parallel to the outcomes and demographic trends described in this review [23]. Machado I et al., emphasised the histological heterogeneity and the need for a comprehensive immunohistochemistry panel, as overlap with other pleural tumours may lead to frequent misdiagnosis [24]. Li Z et al., indeed provided robust cohort data confirming the limited efficacy of current therapeutic approaches and stressed the urgent need for molecular stratification to guide targeted treatment [31]. These findings suggest that an algorithmic approach, incorporating advanced imaging, comprehensive immunophenotyping, and molecular diagnostics at the time of initial evaluation, may significantly reduce diagnostic delays and improve stratification for personalised therapy, thereby offering the potential to enhance overall outcomes for this rare malignancy.

The demographic profile of PPA is biased towards older patients, presenting usually in the sixth or seventh decade of life, with a mild predominance in males. It conforms to the overall epidemiology of angiosarcomas, with an increasing incidence in older people. Symptoms are non-specific, with the most common presentations being chest pain, dyspnoea, cough, and systemic symptoms such as fatigue or weight loss [55]. Haemorrhagic pleural effusion, although not pathognomonic for PPA, is a common finding and may be an early clue when it occurs in the absence of infection or trauma. Early clinical suspicion is still a challenge due to the similarity of symptomatology with other pleural disorders, such as mesothelioma or metastatic carcinomas [56].

While helpful in evaluating thoracic disease, radiologic imaging is non-diagnostic for PPA. CT scans may detect pleural masses, thickening, or effusions; however, these findings are nonspecific. MRI, while MRI, while superior at soft-tissue delineation, is non-diagnostic for differentiating cancers [57]. PET-CT scans may reveal hypermetabolism, but this finding is nonspecific because increased uptake is common to many malignancies and inflammatory conditions. Imaging is more for staging and procedural planning than for diagnosis. The inability of radiologic modalities to reliably diagnose PPA underscores the need for histological confirmation [58].

Cytologic examination of pleural fluid, the initial step in diagnosis in most conditions, is also generally uninformative in PPA. Effusion specimens are typically acellular or necrotic; if present, malignant cells can be challenging to distinguish from reactive mesothelial cells or carcinoma cells. Therefore, there are numerous false negatives or misclassifications [59]. Thus, tissue biopsy remains the gold standard for diagnosis. Thoracoscopic biopsy, particularly via VATS, is ideal because it allows targeted sampling of suspicious areas and yields adequate tissue for histologic and IHC analysis [60].

Histopathologically, PPA exhibits a broad range of morphologies, from spindle cell architecture to an epithelioid pattern. Some tumours develop rudimentary vascular channels, while others are solid sheets of undifferentiated cells. Mimicry of other pleural neoplasms, most notably mesothelioma and metastatic adenocarcinoma, necessitates an IHC diagnosis [61]. Vascular markers CD31, ERG, and FLI-1 are crucial for determining endothelial differentiation. CD34, while helpful, is nonspecific and can be positive in other soft-tissue tumours. CK expression in epithelioid variants can lead to diagnostic pitfalls, especially if endothelial markers are not included in the IHC panel. A panel approach is necessary to rule out misdiagnosis and allow for correct classification [62].

Treatment of PPA is not codified, and current treatment is usually extrapolated from that of soft-tissue angiosarcoma elsewhere in the body. Surgical resection, which is potentially curative in localised disease, is generally not feasible because most cases present later. Even with surgery, recurrence is unavoidable, and long-term survival is rare [63]. Chemotherapy is of limited benefit; taxanes, such as paclitaxel, and anthracyclines, such as doxorubicin, are most frequently used but typically produce only partial remissions or temporary disease stabilisation. Resistance and rapid disease progression are common, which can truncate the duration of response. Radiotherapy is usually palliative to stabilise local symptoms such as pain or bleeding within the chest wall, but it is not curative and is rarely used as a single modality [64].

There has been recent interest in targeted and immunotherapy approaches. PD-1 inhibitors have shown promising activity in cutaneous and cardiac angiosarcomas and may be used in pleural forms. These agents have been theoretically employed in PPA, as no clinical trials are available. Molecular profiling and next-generation sequencing can reveal actionable mutations, but these are not currently standard practice. With the aggressive clinical behaviour and failure of available therapy, it is essential to establish new therapeutic approaches to PPA [65].

Prognostically, PPA carries inferior outcomes. Median survival times in the literature are typically three to six months, despite the use of multimodal, aggressive therapy. Contributing to this poor prognosis are delays in diagnosis, aggressive tumour growth, high recurrence rates, and the absence of effective systemic therapy. Tumours with high mitotic activity, necrosis, and pleural invasion have inferior outcomes. However, early-stage resectable tumours may offer only a limited survival benefit, though this is the exception rather than the rule [66].

There are still significant knowledge gaps in the biological behaviour of PPA. Because of the rarity of PPA, large prospective trials are not available, and data from single-institution series or case reports predominate. These data are prone to referral and selection biases and are limited in generalisability, hindering evidence-based guideline development. Furthermore, the pathogenesis of PPA is poorly understood, with limited knowledge of the molecular changes underlying its aggressive phenotype. The lack of a validated prognostic model also hampers risk stratification and personalised treatment planning [67].

A multidisciplinary research approach will be required to improve understanding and control of PPA. Multicentre registries, when collaboratively collected, may facilitate the collection of clinical data, enabling stronger analysis of treatment responses and prognostic variables. Molecular and genomic studies may reveal new biomarkers and treatment targets. Awareness by the clinician, pathologist, and radiologist at the bedside is necessary to avoid delay in diagnosis. Earlier, a more accurate diagnosis may provide opportunities for access to clinical trials and treatment with novel therapies proven to be effective in related sarcoma subtypes [68].

In short, PPA is one of the most challenging tumours affecting the pleura because of its rarity, nonspecific clinical presentation, histologic heterogeneity, and lack of effective therapy. A very high degree of suspicion, preliminary tissue biopsy, and extensive histopathological evaluation are essential in arriving at a correct diagnosis. While treatments remain suboptimal, advances in tumour biology and new immunotherapeutic agents offer cautious hope for improved prognosis. Continuation of clinical vigilance and research activities is critical in altering the otherwise grim course of this uncommon but lethal cancer.

Emerging Clinical Strategies in Rare Malignancy

The PPA requires new and personalised approaches to management due to extremely low prevalence, rapid biological progression, and poor prognosis. Tumour board participation: Multidisciplinary Tumour board interaction is recognised as necessary and allows early diagnosis, facilitating diagnosis via VATS-guided biopsy, and thorough IHC analysis, including endothelial markers (CD31, ERG and FLI-1). Such a team-based approach allows making timely therapeutic decisions and minimises diagnostic delays, which are often observed in rare thoracic malignancies [69,70].

In addition to the traditional management of the disease, which includes surgical resection, chemotherapy with taxane or anthracycline, and adjuvant radiotherapy, new systemic therapies have emerged and shown promising results in isolated instances [71]. Immune checkpoint inhibitors, especially PD-1 agents such as pembrolizumab, have demonstrated disease stabilisation in epithelioid forms of PPA, and combination immunotherapy with nivolumab and ipilimumab has been shown to reduce tumour burden and malignant pleural effusion in Programmed Death-Ligand 1 (PD-L1)-positive tumours. Clinical trials are also ongoing to determine the synergistic effect of beta-blockers, including propranolol, in combination with immunotherapy for advanced angiosarcoma [72].

The development of molecular diagnostics, especially next-generation sequencing, has enabled the identification of actionable genetic changes, including PIK3CA mutations, with opportunities to apply targeted therapy based on extrapolated treatment regimens from other forms of angiosarcoma [73]. Creation of multicentre registries and universal diagnosis and treatment guidelines can facilitate data pooling, support prospective clinical trials, and hasten the development of individualised treatment plans. With a median survival of less than six months in most series, palliative care early in the comprehensive care cannot be ignored, as it is aimed at symptom management and quality optimisation of life [74].

Prognostic Factors and Future Directions for Management of PPA

The PPA is poorly prognosticated, mainly because of the aggressive nature of the tumour, indeterminate diagnosis, and resistance to therapy. The median survival, as reported, is three to six months from diagnosis despite multimodal treatment. Prognostic markers are poorly defined because most evidence comes from solitary case reports and small series [75].

The most critical factors with poor prognosis are delay in diagnosis, widespread pleural involvement, haemorrhagic effusions, and distant metastasis at presentation. High mitotic rate and epithelioid-type tumours are more aggressive. Refractoriness to primary chemotherapy and inoperability also predict poor outcomes. In rare instances, with early diagnosis at the localised disease stage and resectability, survival has been mildly prolonged; however, this is not typical [76].

The recurrence pattern is frequent, even after surgery or multimodality therapy. The relapse pattern is typically locoregional, but distant metastasis to the lung, bone, or liver can also occur. There is no evidence-based scoring system for predicting prognosis in PPA; thus, individualised risk stratification is not straightforward. There is a significant lack of clinical and translational studies on PPA [77]. Limited molecular characterisation studies exist, making the development of targeted therapies a challenge. Immune checkpoint and angiogenesis inhibitors are newer modalities being explored in other angiosarcoma subtypes and may have future potential in pleural cases. Overall, PPA optimisation will require earlier diagnosis, multicentre data sharing, and the integration of molecular profiling into treatment decision-making to enable individualised, optimised treatment strategies [78].

Key Takeaways

The PPA is an uncommon malignant tumour with a non-characteristic presentation and unfavourable prognosis. Imaging is functional but not diagnostic; diagnosis is by biopsy and immunohistochemistry. Treatment is still limited, and the prognosis is still unfavourable with multimodal therapy. New immunotherapy and molecular therapy are promising for the future. Early diagnosis and a high level of clinical suspicion are required. More data gathering, joint research, and new treatment are needed as an urgent priority to enhance survival in this underdiagnosed but fatal thoracic malignancy.

CONCLUSION(S)

The PPA is a rare and aggressive endothelial neoplasm with severe diagnostic and therapeutic problems. Its nonspecific radiologic and clinical presentation results in delayed diagnosis, while cytology alone is inadequate for diagnosis. Histopathologic proof, confirmed by immunohistochemistry, is required for accurate identification. Even multimodal therapy, such as surgery, chemotherapy, and radiotherapy, produces poor prognoses with limited survival benefits. The tumour's rarity has discouraged the establishment of uniform treatment protocols or large-scale clinical trials. However, the increasing interest in targeted therapies, immunotherapy, and improved molecular characterisation provides a potential route for future advancement. Increased awareness, early tissue sampling, and multidisciplinary treatment are essential for early diagnosis and management. The present narrative review highlights the need to explore novel therapeutic modalities

and large-scale clinical registries to improve the understanding and management of this highly lethal pleural tumour.

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