Review Article

Biological characteristics and clinical treatment of pulmonary sarcomatoid carcinoma: a narrative review

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Background and Objective: Pulmonary sarcomatoid carcinoma (PSC) is a subset of non-small cell lung cancer (NSCLC) with highly malignant, aggressive, and heterogeneous features. Patients with this disease account for approximately 0.1–0.4% of lung cancer cases. The absence of comprehensive summaries on the basic biology and clinical treatments for PSC means there is limited systematic awareness and understanding of this rare disease. This paper provides an overview of the biological characteristics of PSC and systematically summarizes various treatment strategies available for patients with this disease.

Methods: For this narrative review, we have searched literature related to the basic biology and clinical treatment approaches of PSC by searching the PubMed database for articles published from July 16, 1990 to August 29, 2023. The following keywords were used: "pulmonary sarcomatoid carcinoma", "genetic mutations", "immune microenvironment", "hypoxia", "angiogenesis", "overall survival", "surgery", "radiotherapy", "chemotherapy", and "immune checkpoint inhibitors".

Key Content and Findings: Classical PSC comprises epithelial and sarcomatoid components, with most studies suggesting a common origin. PSC exhibits a higher tumor mutational burden (TMB) and mutation frequency than other types of NSCLC. The tumor microenvironment (TME) of PSC is characterized by hypoxia, hypermetabolism, elevated programmed cell death protein 1/programmed cell death-ligand 1 expression, and high immune cell infiltration. Treatment strategies for advanced PSC are mainly based on traditional NSCLC treatments, but PSC exhibits resistance to chemotherapy and radiotherapy. The advancement of genome sequencing has introduced targeted therapies as an option for mutation-positive PSC cases. Moreover, due to the characteristics of the immune microenvironment of PSC, many patients positively respond to immunotherapy, demonstrating its potential for the management of PSC.

Conclusions: Although several studies have examined and assessed the TME of PSC, these are limited in quantity and quality, presenting challenges for research into the clinical treatment strategies for PSC. With the emergence of new technologies and the advancement of clinical research, for example, savolitinib's clinical study for *MET* exon 14 skipping mutations positive PSC patients have shown promising outcomes, more in-depth studies on PSC are eagerly anticipated.

Keywords: Pulmonary sarcomatoid carcinoma (PSC); biology; clinical characteristics; treatment strategies

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Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare type of non-small cell lung cancer (NSCLC) with a poor prognosis even when diagnosed at early stages (1) and usually occurs in older males (2). According to the 2021 World Health Organization (WHO) classification, PSC can be classified as pulmonary pleomorphic carcinoma (PPC), spindle cell carcinoma (SCC), giant cell carcinoma (GCC), carcinosarcoma, and pulmonary blastoma (PB) (3). The complex composition of PSC arises from the coexistence of epithelial and sarcomatoid components, varying in proportions and types within the tumor tissue. The origin of these complex components is essential for understanding PSC and developing therapeutic strategies against it. Nevertheless, the rarity of PSC and its intra- and inter-tumor heterogeneity present substantial challenges in clarifying its biological characteristics.

The treatment for advanced PSC has followed the standard first-line approach for NSCLC, yet the outcomes have proven unsatisfactory, and PSC exhibits high resistance to chemotherapy and radiotherapy (4). For patients with NSCLC, directed targeted therapies based on aberrant gene mutation have significantly improved survival (5). There is a significant amount of evidence indicating that PSC has a high mutation frequency (6,7), and thus targeted therapy for mutation-positive patients may have considerable potential. Additionally, immune checkpoint inhibitors (ICIs) have yielded promising results in NSCLC in recent years, and PSC exhibits a high level of immune infiltration and expression of immune checkpoints (8). Overall, immunotherapy, particularly the administration of ICIs, represents a new hope for patients with PSC.

In this paper, we discuss the histologic transformation, genetic characteristics, metabolism, and immune microenvironment of PSC, and review various therapeutic strategies, including chemotherapy, targeted therapy, and immunotherapy. We hope to provide insight and promote a need for a deeper understanding of this rare and highly malignant lung tumor. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-127/rc).

Methods

We have systematically searched the PubMed database using the following search terms: "pulmonary sarcomatoid carcinoma", "genetic mutations", "immune microenvironment", "hypoxia", "angiogenesis", "overall survival", "surgery", "radiotherapy", "chemotherapy", and "immune checkpoint inhibitors". Only original articles published in English, including research articles and literature reviews, were included in this review (*Table 1*).

Biology of PSC

Origin and histological transformation

PSC has gained much attention due to the coexistence of its epithelial and sarcomatoid components. As early as 1863, Virchow initially described carcinosarcoma and posited a theory concerning the origin of its two components: they either occur separately and later intermix, or one component transforms into another during tumor development (9). Over time, it became the prevailing belief that PSC originated from carcinoma, with the epithelial components dedifferentiating into the sarcomatoid components. The transition areas from carcinoma to sarcomatoid component were revealed by light and electron microscopy (10).

There have been reports in some individual patients of transformation from common NSCLC to PSC (11-13) or even from SCLC to PSC (14,15). The morphology and immunohistochemistry of PSC also suggest an NSCLC origin, typically the lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC) subtypes (16). Vieira *et al.* explored the possible origin of PSC by immunohistochemical analysis of thyroid transcription factor 1 (TTF1) expression in LUAD and P63 expression in LUSC, reporting that 41.5% and 17% of the PSC cases originated from LUAD and LUSC, respectively (17). Through whole-exome sequencing (WES), Yang *et al.* analyzed the somatic mutations and copy number variations (CNVs) in 56 patients with PSC and found clonal correlations between two components in all patients by calculating the tumor clonality index (CI) (8). These results suggested a common origin of the epithelial and sarcomatoid components of PSC (8).

Epithelial-mesenchymal transition (EMT) plays a crucial role in tissue fibrosis, cancer development, progression, and metastasis (18-20). Cells lose cell adhesion and polarity, acquiring mesenchymal features that are similar to the morphology and migratory capacity of spindle cells (21). The coexistence of the more differentiated epithelial component and the less differentiated sarcomatoid component potentially suggests that PSC originates from the transition of malignant epithelial cells into a mesenchymal phenotype (22-24). Several studies have

Table 1 Summary of the search strategy

Items	Specification
Date of search	August 29, 2023
Databases and other sources searched	PubMed
Search terms used	"pulmonary sarcomatoid carcinoma", "genetic mutations", "immune microenvironment", "hypoxia", "angiogenesis", "overall survival", "surgery", "radiotherapy", "chemotherapy", "immune checkpoint inhibitors"
Timeframe	Studies published from July 16, 1990 to August 29, 2023
Inclusion and exclusion criteria	Inclusion criteria: English language and original publications, including research articles and literature reviews
	Exclusion criteria: non-English language and no full-text available
Selection process	Study selection and assessment were conducted by the first author Y.W. and the other authors consented to the selection process

shown that PSC undergoes an EMT process (25-27). In one study, transcriptomic data from the 195 differentially expressed genes (DEGs) of both components primarily displayed enrichment in epithelial, mesenchymal features, and EMT-related pathways (8). Manzotti *et al.* analyzed 146 differential genes using Gene Ontology enrichment analysis, which identified sarcomatoid components enriched for downregulated genes mainly related to cell adhesion and epithelial differentiation during the epithelial-to-sarcomatoid transition (28); and enriched for upregulated genes involved in extracellular interactions and angiogenesis (28). DNA methylation data also supports a connection between PSC and EMT, indicating the potential involvement of DNA methylation in EMT regulation (8).

Immunohistochemical research suggests that the expression of EMT-related markers such as E-cadherin, vimentin, Twist-related protein 1 (Twist1), Zinc finger E-box-binding homeobox 1 protein (ZEB1), Slug, Snail, c-Jun, and vasculogenic mimicry (VM) are increased in PSC compared to LUSC (29-32). ZEB1 is sensitive and highly specific for PSC diagnosis (33), predicting a poor prognosis (31). There is no difference in immunohistochemical vimentin expression between PSC biopsy and surgical specimens, indicating the prevalence of the EMT process in PSC (34). In addition, the PSC EMT process may be connected to integrin-related pathways, with Shimizu *et al.* suggesting that overexpression of fibronectin mediated by the integrin ligase kinase (ILK) signaling pathway contributes to the EMT transformation of PSC (35).

Overall, most evidence supports a common origin of PSC's complex histologic composition, with EMT figuring prominently in this process. However, further research is still needed to confirm these conclusions.

Genetic characteristics

PSC exhibits a high mutation level (6,7) compared to other NSCLC subtypes (36,37) (*Figure 1*). In their study, Schrock *et al.* reported that the mean tumor mutational burden (TMB) of PSC of 13.6 mutations per megabase (Mb), with 20% of cases having a TMB of >20 mutations/Mb and 43% having a TMB of >10 mutations/Mb (38). The WES results from Liu *et al.*'s analysis of 10 cases included a total of 1461 somatic mutations, of which 58.2% were missense mutations, 27.0% silent mutations, 5.3% deletion mutations, 5.2% nonsense mutations, 2.3% insertion mutation, 1.8% splice-site mutations, and 0.3% stop-loss mutations (39). Patients with a smoking history are more likely to carry mutations (17), and the high mutation rate of PSC may be related to genetic instability due to tobacco exposure (40).

The most frequent mutations in PSC are tumor protein 53 (*TP53*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), epidermal growth factor receptor (*EGFR*), and mesenchymal to epithelial transition factor (*MET*) (7,8,17,36-38,41-44). Yang *et al.* performed comprehensive WES of 56 patients with PSC (8). It was found that *TP53* was the most common mutation (44/56), 57% of patients carried mutations in the RTK/RAS pathway gene, 16% in *EGFR*, 14% in *KRAS*, 13% in *MET*, 7% in *BRAF*, 5% in *NF1*, and 4% in *NRAS*. Most *EGFR* mutations, such as exon 19 deletion and exon 21 L858R, were common

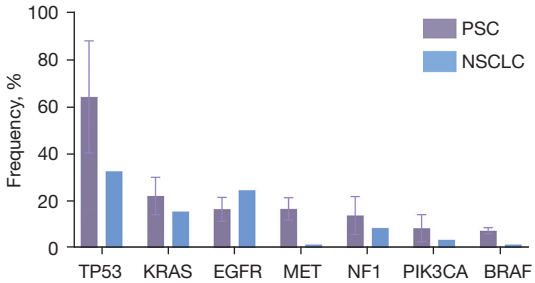

Figure 1 Comparison of mutation frequencies between PSC and NSCLC. PSC gene mutation frequency is summarized from the reference literature in the Mutation Characteristics section of the main text, with error bars indicating variations in mutation frequency at the same mutation site in PSC across different studies. The data on NSCLC mutation frequency is sourced from the COSMIC database (https://cancer.sanger.ac.uk/cosmic). PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small cell lung cancer; *TP53*, tumor protein 53; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal to epithelial transition factor; *NF1*, neurofibromatosis type 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; COSMIC, catalogue of somatic mutations in cancer database.

and targetable. *KRAS* mutations mainly involved codon 12. *MET* mutations were mostly *MET* exon 14 skipping alterations. Mutations in the phosphatidylinositol 3 kinase (PI3K) pathway were present in 27% of patients: 13% were *PIK3CA*, 9% *PTEN*, 5% *AKT3*, and 2% *AKT1*. Schrock *et al.* detected 125 mutated genes in formalin-fixed paraffin-embedded (FFPE) PSC samples, including *TP53* (74%), *KRAS* (34%), *MET* (13.6%), *EGFR* (8.8%), *BRAF* (7.2%), *HER2* (1.6%), and *RET* (0.8%) (38). Fallet *et al.* tested 114 surgical samples, revealing that the most common mutations were *KRAS* (27.2%), *EGFR* (22.2%), *TP53* (22.2%), *STK11* (7.4%), *NOTCH1* (4.9%), *NRAS* (4.9%), and *PI3KCA* (4.9%) (7). The variability in mutation sites and frequencies detected across different panels reflects differences in sample size and the sensitivity of detection methods.

Biphasic PSC represents the most prevalent subtype of PSC. To investigate the homogeneity and heterogeneity of gene mutations between the two components of biphasic PSC, Liu *et al.* performed laser capture microdissection and next-generation sequencing (NGS) on 31 PSC samples (45). The most frequently altered genes in epithelial components were *TP53* (74%), *MET* (19%), *EGFR* (19%), *KRAS* (19%), *NF1* (19%), and *MAP3K1* (19%); meanwhile, the most frequently altered genes in sarcomatoid components were *TP53* (74%), *MET* (23%), *EGFR* (19%), *KRAS* (19%), and *NF1* (19%). Notably, 97% of patients exhibited common mutations and frequencies in both components. Similarly, WES analysis of 15 cases by Pécuchet *et al.* demonstrated that the most common driver mutations in PSC are predominantly in the main clonal population, with subclonal populations accounting for less than 10% (46), implying a monoclonal origin of PSC.

Metabolic microenvironment

It is well known that a hypoxic tumor microenvironment (TME) is an inherent feature of solid malignant tumors and is widely recognized as an independent indicator of poor prognosis (47,48). Hypoxia affects various aspects of tumor cell metabolism and angiogenesis, promoting tumor heterogeneity and plasticity (47,49,50). Compared with other NSCLC subtypes, PSC has a higher level of hypoxia (51).

Hypoxia-inducible factor (HIF), a heterodimer with multiple isoforms (52), predominantly includes HIF-1α, which is responsible for activating transcriptional responses under hypoxic conditions and promoting tumor progression (53). Chang *et al.* assessed the expression of HIF-1α in 122 cases of PPC, with 92 (75.4%) displaying the overexpression of HIF-1α (54). The expression was concentrated in the nucleus of the perinecrotic region of the sarcoma component (54). In an analysis of 55 cases each of PPC and LUAD, Tsubata *et al.* found that the HIF-1α expression levels were significantly higher in PPC than in LUAD (P=0.03) (51). Multivariate analysis in another study suggested that extensive tumor necrosis is an independent prognostic factor for PSC (55). These findings are consistent with the clinical observation that PSC tends to involve a larger tumor size and is associated with more necrotic components.

Under a hypoxic environment, tumor cells adapt by autonomously altering various metabolic pathways, such as that seen in the Warburg effect, to meet their increased bioenergetic and biosynthetic needs (56). HIF-1α performs an important role in redirecting glucose metabolism patterns from oxidative phosphorylation to glycolysis in tumor cells (57).

PSC is considered to be a type of cancer with high metabolic levels. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), a valuable diagnostic tool for malignant tumors

based on glucose metabolism, has confirmed the high glucose metabolism levels in the PSC (58). The reported standardized uptake values (SUVs) for the positron emission tomography of ^{18}F-FDG in patients with PSC tend to be high (median 19.3) (59), which is significantly higher than those of other NSCLC subtypes (60,61).

Enhanced glucose uptake in tumor cells is facilitated by glucose transporter carriers (62), which have significantly increased in tumor tissues (63,64). HIF-1α can induce the expression of glucose transport proteins such as glucose transporter 1 (Glut1) and Glut3 (57). The overexpression of Glut1 in human tumors is closely related to 18F-FDG uptake (65,66). Research indicates higher Glut1 expression in undifferentiated cancers compared to well-differentiated cancers (67), as in PSC. In one study, immunohistochemical staining of 104 patients with PSC revealed that 48% of samples had a high Glut1 expression, which was significantly associated with vascular infiltration and tumor cell proliferation (68). Additionally, the univariate analysis indicated that Glut1 was a significant predictor of poorer postoperative overall survival (OS), with those patients showing high Glut1 expression experiencing a worse prognosis than those with low expression (68).

Angiogenesis and vascular invasion are critical biological processes in tumor development and metastasis (69-73). The balance between proangiogenic and antiangiogenic factors is disrupted during tumor development due to hypoxia and an insufficiency in metabolic substances (74). HIF induces the expression of several proangiogenic factors, such as vascular endothelial growth factor (VEGF) and VEGF receptor (75).

Microvessel density (MVD) can be used to assess tumor angiogenesis, which correlates with the expression of angiogenic factors, such as VEGF, and is predictive of a poor prognosis in NSCLC (76,77). In an analysis of 55 cases each of PPC and LUAD, Tsubata *et al.* found that MVD expression levels were significantly higher in PPC than in LUAD (P=0.03) (51). Hypoxia-induced overexpression of HIF-1α activates VEGF transcription, leading to a poorer prognosis and increased chemoresistance (78,79), which is a potential cause of the chemoresistance in PSC. The incidence of vascular invasion in NSCLC is usually 30–50% (55,80,81) but is 90% in patients with PSC (82). Vascular invasion can be an independent factor for poor prognosis (17,83).

PSC is a hypoxic and hypermetabolic type of tumor, with frequent angiogenesis and vascular invasion. These characteristics are also relevant to therapy resistance (54). Hence, comprehensively characterizing the metabolic features of PSC, along with its two components, is critical to devising effective treatments.

Immune microenvironment

The composition of the tumor immune microenvironment (TIME) is integral to governing tumor-immune interactions. Most studies point to PSC being a "hot tumor". Moreover, a higher TMB and leukocyte fraction indicate a T cell-inflamed microenvironment in the PSC (8).

Programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1), the most important immune checkpoint, has a high expression in PSC (84,85). In one study, the immunohistochemical results for PD-L1 were positive in 95% of patients, with a median PD-L1 expression of 70% (37). Kim *et al.* assessed PD-L1 expression in patients included in a clinical trial (NCT03022500), with 64.3% of the patients exhibiting PD-L1 expression ≥50% (41). PD-L1 expression is higher in the sarcomatoid component compared to the epithelial component (86-88). In the multivariate analysis of one study, high PD-L1 expression correlated with a better prognosis (89). Zhou *et al.*'s study revealed that the PD-L1 tumor proportion scores (TPSs) of <1%, 1–49%, and ≥50% corresponded to overall response rates (ORRs) of 33.3%, 72.7%, and 85.7%, and median progression-free survival (PFS) of 6.0, 6.7, and 10.3 months, respectively (90). In a different study, a higher TMB compared to a lower TMB was correlated with higher PD-L1 expression and median OS (18 *vs.* 1.84 months) (37).

Lymphoid and myeloid cells constitute the majority of immune cells in the TME. Vieira *et al.* reported that the expression level of CD3 was higher in PSC than in NSCLC, suggesting greater T-cell infiltration in PSC (91). Immunohistochemistry in another study confirmed the enrichment of $CD8^+$ T cells in the PSC (92). Meanwhile, Zhang *et al.* reported that PD-L1 expression was positively correlated with $CD8^+$ T-cell infiltration in patients with PSC (93). Tumor infiltration $CD8^+$ T is more prevalent in PD-L1-positive patients with PSC than in PD-L1-negative patients (87). Chen *et al.*'s analysis of FFPE samples from 100 patients found that those with higher levels of $CD8^+$ T-cell infiltration experienced better prognosis than did those with lower levels of infiltration (mean OS 92.3 *vs.* 31.2 months; P<0.05) (94). In analyses of the baseline circulating lymphocyte composition of PSC, patients who experienced treatment benefits had a higher proportion of $CD8^+$ T cells compared to those who did not receive

benefits (41).

Myeloid cells also extensively infiltrate PSC. Immunohistochemistry suggests that tumor-associated macrophages (TAMs) are enriched in PSC (91,95), which is potentially related to the EMT process. In one study, $CD163^+$ macrophages (M2 type) showed greater infiltration in PSC than in NSCLC and correlated with high PD-L1 expression (91). Furthermore, an elevated neutrophil-to-lymphocyte ratio (NLR) in peripheral blood correlates with poorer PSC prognosis (96). As for the difference in immune infiltration of two components of PSC, Yang *et al.* conducted a fluorescent multiplex immunohistochemical analysis of PD-L1, CD4, CD8, CD68, and FoxP3 between the two components of PSC and found no significant difference between them (8).

Some studies have performed immunophenotyping to investigate the immune microenvironmental characteristics of PSC. Ma *et al.* classified 32 patients with PSC into three types based on their infiltration with CD8+ T cells in different spatial regions (intratumoral and peritumoral regions), classifying 65.6%, 15.6%, and 18.8% as immune-inflamed, immune-excluded, and immune-desert, respectively. (92) Combining intratumoral $CD8^+$ T-cell infiltration and the TPS of PD-L1 staining in the intratumoral region, they then classified patients into four types: type I ($PD\text{-}L1^+/CD8^+$: adaptive immune resistance), type II ($PD\text{-}L1^-/CD8^-$: immunologic ignorance), type III ($PD\text{-}L1^+/CD8^-$: intrinsic induction), and type IV ($PD\text{-}L1^-/CD8^+$: tolerance). The type I immunophenotype was the most common subtype in PSC, accounting for 46.9% of patients (92). Yang *et al.* generated three clusters of patients with PSC based on DNA methylation data, with the cluster that was most enriched in patients having the lowest level of DNA methylation and the greatest degree lymphocyte infiltration (8).

As PSC is a hot tumor, with rich infiltration of immune cells and high expression of immune checkpoints, it likely has an adaptive immunosuppressive microenvironment. Therefore, the prospects for immunotherapy, particularly ICIs, are promising for patients with PSC.

Clinical characteristics and treatment

Clinical characteristics

PSC tends to occur in older males with a smoking history (4,37,93,97). Patients are often diagnosed at an advanced tumor stage (98) and are accompanied by clinically significant symptoms (2), including cough, sputum, hemoptysis, chest pain, and weight loss. PSC usually has a large tumor size (99), with marked central necrosis (100). Imaging diagnostics frequently reveal a central low attenuation area or cavity (101). Biphasic tumors (4,102), particularly PPC, are more prevalent in PSC (2,7,103). Metastases occur early and frequently in patients with PSC, with the common sites being similar to those of NSCLC (adrenal glands, lungs, pleura, brain, bone, or liver). Over half of the patients with PSC exhibit metastases in more than two locations (4,100). The median OS for patients with PSC is approximately 6.3 months, while the median PFS is 2 months (37). The 1-, 2-, and 5-year survival rates are approximately 42%, 23%, and 15%, respectively (98).

Surgical treatment

Patients with early-stage lung cancer, including PSC, can benefit from surgical treatment. The survival and prognosis of patients with PSC who undergo surgical treatment are significantly better than those who do not (59,104). In a retrospective analysis of 400 patients with PSC from the Surveillance, Epidemiology, and End Results (SEER) database, Xie *et al.* found that patients who received surgical treatment exhibited a more favorable prognosis compared to those who did not [hazard ratio (HR) =1.43] (105). Moreover, the median survival time was better in postoperative patients (23.0 *vs.* 11.0 months; P=0.016) (104). It is worth noting that the 5-year survival rate for postoperative patients with PSC ranges from 11% to 24.5% (106), which is lower than that of patients with other types of NSCLC, suggesting the highly malignant and aggressive nature of PSC.

For patients with early-stage PSC, surgical treatment is the preferred treatment approach. However, a significant proportion of patients with PSC are not suitable for surgery, making medical therapy a necessary option. PSC is associated with a high postoperative recurrence risk and thus has a shorter survival time compared with other types of NSCLC. Consequently, it is critically important to consider adjuvant therapy following surgery.

Chemotherapy

For resectable NSCLC, surgery remains the most essential treatment strategy, while chemotherapy or radiotherapy serves as adjuvant therapy. For advanced NSCLC, chemotherapy nonetheless retains an indispensable role. However, several cases suggest that PSC is insensitive to chemotherapy (58,107-109).

First-line chemotherapy

In a retrospective study with 71 advanced patients with PSC receiving first-line chemotherapy, 73% received platinum-based chemotherapy (4). The outcomes showed that 16.5% of patients achieved a partial response (PR), 14.5% had stable disease (SD), and 69% experienced disease progression (PD) (4). Among all patients, the median PFS was 2.0 months, and the median OS was 6.3 months (4), which was lower compared to that of other NSCLC subtypes (In three randomized studies of 984 patients with non-PSC NSCLCs, the median PFS was 4.3 months, and the median OS was 8.9 months) (110). Another retrospective study included 28 patients with advanced or recurrent PSC, 85% of whom received platinum-based therapy (2). In this cohort, the ORR was 7%, 21% had SD and 72% exhibited PD (2). The median time to progression (TTP) was 2.7 months, and the median OS was 4.3 months (2). A phase II study investigating carboplatin plus paclitaxel with or without bevacizumab enrolled 16 patients with PSC. Among them, seven patients received carboplatin plus paclitaxel alone, resulting in a 0% ORR (SD: 2; PD: 4; not evaluable: 1), a median PFS of 1.2 months, and a median OS of 7.9 months (111). In another study, patients treated with platinum-based chemotherapy had a better OS than those treated with non–platinum-based chemotherapy (7.0 *vs.* 5.3 months; P=0.096) (4), which was corroborated by another study (5.6 *vs.* 1 month) (2). The multivariate analysis of the former study indicated that platinum-based chemotherapy (HR =0.92) was associated with better OS than non–platinum-based chemotherapy (4).

Targeting the sarcomatoid component may be a viable strategy for PSC treatment. The regimen of combined chemotherapy, including mesna, doxorubicin, ifosfamide, and dacarbazine (MAID), has demonstrated efficacy in soft tissue sarcoma (112,113). There are reports of positive responses in patients with PSC treated with this regimen (114). Lee *et al.* retrospectively analyzed 17 patients with PSC treated with MAID and reported an ORR of 35%, a median PFS of 2.8 months, and a median OS of 8.7 months (115). Therefore, developing therapeutic strategies that specifically target the sarcomatoid component has potential in treating PSC.

Perioperative chemotherapy

Although perioperative chemotherapy has yielded improved rates of complete surgical resection, pathological remission, and survival in NSCLC, its efficacy in PSC remains underreported in prospective studies. A systematic review and meta-analysis indicated that neoadjuvant chemotherapy for NSCLC can reduce mortality by 13% (116). A retrospective study of PSC by Vieira *et al.* involved 20 patients (26%) who received neoadjuvant chemotherapy, with 55% of patients having PR, 40% with SD, and 5% with PD (17). A study from the Mayo Clinic also reported the benefits of neoadjuvant chemotherapy for patients with PSC (98).

Adjuvant therapy has become a standard treatment approach for some types of NSCLC (117), and cisplatin-based postoperative chemotherapy has been shown to improve OS in NSCLC (compared with the control group, the chemotherapy group showed a significant prolongation in OS (94 *vs.* 73 months; P=0.04), with 5-year survival rates of 69% and 54% respectively (P=0.03) (118,119). Surgery is the best treatment choice for patients with early-stage PSC. However, the high risk of postoperative recurrence suggests that adjuvant chemotherapy should be strongly considered. A meta-analysis suggested that patients receiving adjuvant chemotherapy have a significantly longer OS than those treated with surgery alone (120). Abdallah *et al.* compared 1,497 postoperative patients with PSC who received adjuvant chemotherapy with those who did not and found enhanced survival in stage II and III patients; however, stage III cases benefited in particular, with adjuvant chemotherapy resulting in a significant increase in OS from 12% to 30% (121). However, adjuvant chemotherapy was not found to be correlated with improved survival in stage I patients (121). Similarly, other studies suggest that adjuvant chemotherapy does not improve survival in patients with stage I PPC (122), while some have reported that adjuvant chemotherapy does not confer a survival benefit (99); this discrepancy may be due to the patients with different stages being included but not analyzed separately.

First-line chemotherapy demonstrates limited efficacy in PSC. However, perioperative chemotherapy has shown promise in improving survival for some patients (123). The mechanisms of PSC chemoresistance may be related to the sarcomatoid component (124) but remain underexamined, and thus chemotherapeutic strategies targeting the sarcomatoid component may be worth exploring. Overall, the chemotherapy-related treatment strategies in PSC need to be further investigated.

Radiotherapy

Radiotherapy serves as an important local therapeutic

approach for treating patients with NSCLC across all clinical stages. Some studies have reported favorable outcomes among patients with PSC who have undergone radiotherapy (125,126). Gang *et al*. conducted a retrospective analysis of 1,039 patients with PSC using the SEER database and found that radiotherapy was an independent factor associated with a better prognosis for patients with PSC (127). Similarly, Xie *et al.* analyzed 400 patients with PSC and arrived to a similar conclusion (105). However, Rahouma *et al.* analyzed 4,987 patients with PSC and reported a median OS of 5 months for those receiving radiotherapy compared to 6 months for those without radiotherapy (P<0.001) (128). They also compared patients who received both neoadjuvant and adjuvant radiotherapy to those who received only adjuvant radiotherapy, with the median OS being 11 months and 9 months, respectively (128). In the study by Sun *et al.*, patients who received adjuvant radiotherapy had a higher 5-year survival rate than did patients who did not receive treatment (55.4% *vs.* 29.4%; P<0.01) (129). Therefore, the efficacy of radiotherapy in PSC remains controversial, and this can be attributed to confounding variables within studies and the lack of subgroup analysis. Overall, perioperative radiotherapy appears to provide partial benefits to patients with PSC.

Targeted therapy

Targeted therapies mainly comprise small-molecule kinase inhibitors (SMKIs), which inhibit protein kinases involved in the biological processes of cancer cells, and monoclonal antibodies (mAbs), which work by targeting extracellular ligands and membrane receptors (130). The increasingly frequent discovery of novel therapeutic targets is carrying forth NSCLC treatment into the precision era. Given the high mutation frequency in PSC, the potential benefits of targeted therapy seem promising.

EGFR tyrosine kinase inhibitors (TKIs)

The significance of *EGFR* mutations in NSCLC has gained widespread recognition since they were first identified. The frequency of *EGFR* mutations in PSC is still controversial, with some studies suggesting that the frequency of *EGFR* mutations is as high as 20% in Asian populations (26,59), while it is lower in White populations (17,131-133). Types of *EGFR* mutations also vary across different studies. In contrast to the findings of Yang *et al.*, which point to most *EGFR* mutations being common mutations (8), almost all *EGFR* mutations in the study by Fallet *et al.* were rare (88.9%) and were mainly concentrated in exons 2, 18, and 20, with the G719A mutation being the most common (55.5%) (7). More evidence is needed to clarify the role of *EGFR* mutations in PSC.

EGFR TKIs have proven to be effective as treatments for *EGFR* mutation-positive NSCLC, particularly in LUAD (gefitinib *vs.* chemotherapy, mPFS 10.8 *vs.* 5.4 months, P<0.001; erlotinib *vs* chemotherapy, mPFS 13.1 *vs.* 4.6 months, P<0.0001) (134,135). Nevertheless, the effectiveness of EGFR TKIs in PSC remains unclear. In some cases, the outcomes are unsatisfactory, and the clinical progression tends to be more rapid and occasionally accompanied by serious complications. In a case of advanced SCC with an *EGFR* exon 19 deletion mutation, the patient received gefitinib with no observable effect and died of respiratory failure 89 days later (136). Erlotinib was also unsatisfactory. A patient with advanced PPC with an *EGFR* exon 21 L858R mutation died just 1 week after starting erlotinib treatment due to rapid PD (137). Other patients have also not achieved long-term outcomes (138,139), but there are some reports in which EGFR TKIs demonstrated good efficacy (107,140).

The efficacy of EGFR TKIs in PSC remains to be further clarified, but poor efficacy appears to be reported for the majority of cases. Patients who do not respond to EGFR TKIs always tend to have rapid progression with severe complications. Caution should thus be exercised in the selection of treatment strategies for patients with PSC and *EGFR* mutations.

MET TKIs

MET mutations are more prevalent in PSC compared to other types of NSCLC (~3%), especially *MET* exon 14 skipping mutations (38,133,141,142). It has been widely demonstrated that MET TKIs benefit patients with NSCLC and *MET* exon 14 skipping mutations (a multicenter retrospective analysis evaluating the efficacy of MET TKIs indicates that NSCLC patients receiving treatment have a longer mOS compared to those who did not, 25.3 *vs.* 10.9 months) (143,144). Moreover, the efficacy of MET TKI in PSC has been demonstrated in prospective clinical studies.

A multicenter, single-arm, phase II clinical study (NCT02897479) evaluated the efficacy of the MET inhibitor savolitinib in patients with PSC and *MET* exon 14 skipping mutations. The study enrolled 70 patients, including 25 with PSC, treated with savolitinib once daily. The subgroup analysis indicated PR in 10 patients (ORR

of 40.0%), a median duration of remission (DOR) of 17.9 months, and a median PFS of 5.5 months (97). Other clinical studies on MET TKI included only a limited number of patients with PSC. The phase 2 VISION trial reported an ORR of 46% for patients treated with tepotinib (145), while the phase 2 GEOMETRY mono-1 trial reported an ORR of 41% for camatinib in previously treated patients (146). Nonetheless, these trials included only a small fraction of patients with PSC (<8%) and lacked subgroup analyses. Case reports also point to the efficacy of crizotinib in patients with PSC and *MET* amplification (147,148).

Antiangiogenic therapy

Antiangiogenic therapy has become the cornerstone of second-line treatment or beyond for soft tissue sarcoma and the standard first-line treatment for some subtypes of soft tissue sarcoma. The presence of a sarcomatoid component in PSC suggests the potential effectiveness of antiangiogenic therapy.

Antiangiogenic monotherapy, such as that with apatinib or sorafenib, has shown favorable outcomes in case reports (149,150). Antiangiogenic combination therapy has also demonstrated promising results in PSC. For example, paclitaxel plus carboplatin combined with apatinib (151) or bevacizumab (152) both yielded benefits to patients. In one patient with SCC, complete response (CR) was sustained for 35 months after discontinuation of carboplatin plus paclitaxel and bevacizumab (153). A phase II study (UMIN000008707) included 9 patients treated with carboplatin plus paclitaxel alone or combination with bevacizumab. Patients who received combination therapy had an ORR of 44.4% (PR: 4; SD: 3; PD: 2) a median PFS of 4.2 months, and a median OS of 11.2 months, which was significantly superior to those who underwent chemotherapy alone (111). The feasibility of antiangiogenic therapy combined with chemotherapy is highly apparent. Interestingly, a patient with PPC was effectively and safely treated with bevacizumab plus paclitaxel for critical and refractory brain metastases after whole brain radiotherapy (WBRT), suggesting the possible value of radiotherapy combined with bevacizumab in patients with PSC (154). In some case reports, antiangiogenic therapy combined with immunotherapy provided promising results. A chemoresistant patient achieved CR over 20 months after treatment with tislelizumab plus anlotinib (109). Similarly, good efficacy was observed in cases treated with anlotinib combined with nivolumab (155), camrelizumab (156), or pembrolizumab (157).

Given the higher occurrence of angiogenesis in PSC, antiangiogenic therapy, particularly that combined with chemotherapy or immunotherapy, holds considerable promise. The presence of vascular invasion should also be considered during clinical treatment.

Immunotherapy

Immunotherapy mainly revolves around PD-1/PD-L1 and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) inhibitors. PD-1/PD-L1 inhibitors have gained significant interest in the treatment of NSCLC. Their application has expanded from second-line to first-line treatments, from advanced to locally advanced and early stages, and from single-agent application to combination therapies. As previously mentioned, the high expression of PD-L1 and abundant immune infiltration in PSC suggest that immunotherapy will likely be effective in PSC (158). In a few reports, patients with PSC who failed first- and second-line chemotherapy demonstrated positive responses to immunotherapy (159,160).

Regarding the impact of first-line immunotherapy on patients with PSC, a multicenter retrospective study enrolled 21 patients with PSC receiving first-line immunotherapy (161). Of these patients, 14 received immunotherapy combined with anlotinib (tislelizumab: 7; camrelizumab: 4; sintilimab: 2; pembrolizumab: 1), 4 received immunotherapy combined with platinum-based chemotherapy (pembrolizumab: 2; sintilimab: 1; durvalumab: 1), and 3 patients received immune monotherapy (camrelizumab: 2; sintilimab: 1) (161). The ORR was 57.1%, the disease control rate (DCR) was 81% (PR: 12; SD: 5; PD: 4), the median PFS was 9.2 months, and the median OS was 22.8 months (161). Immune monotherapy, immunotherapy combined with anlotinib, and immunotherapy combined with chemotherapy yielded a median PFS of 8.0, 9.4, and 9.6 months, respectively, while the median OS was 19.0, 22.8, and 30.6 months, respectively (161). No statistical differences in PFS or OS were observed between treatment strategies or different ICIs (161). Wei *et al.* reviewed 33 patients who received immune monotherapy (8 patients) or immune combination therapy (25 patients; immunotherapy combined with chemotherapy or targeted therapy) as first-line (19 patients) or second-line (14 patients) treatment. Among all patients, the ORR was 36.4% and the DCR was 78.8%. The median PFS and OS were 6.07 and 21.33 months,

Table 2 Completed and ongoing clinical trials of PSC

Trial number	Study type	Study phase	Therapeutic agent	Primary outcome	Start of enrollment	Study status
NCT04888429	Interventional	Phase II	Camrelizumab + famitinib	ORR	2021/7/19	Recruiting
NCT04725448	Interventional	Phase II	Toripalimab + bevacizumab + nab-paclitaxel + carboplatin	PFS	2021/4/6	Recruiting
NCT04224337	Interventional	Phase II	Durvalumab + doxorubicin + ifosfamide	RR	2020/6/11	–
UMIN000027629	Interventional	Phase II	Pembrolizumab	OR	2017/6/12	No longer recruiting
NCT03022500	Interventional	Phase II	Durvalumab + tremelimumab	RR	2017/5/18	–
NCT02834013	Interventional	Phase II	Ipilimumab + nivolumab	ORR	2017/1/13	Active, not recruiting
NCT02897479	Interventional	Phase II	Savolitinib	ORR	2016/12/1	–
UMIN000023433	Interventional	Phase II	Nivolumab	OR	2016/11/1	No longer recruiting
UMIN000008707	Interventional	Phase II	Carboplatin + paclitaxel + bevacizumab/ carboplatin + paclitaxel	RR	2012/8/17	–
NCT05337163	Observational	–	–	–	2022/2/25	Recruiting
NCT04215913	Observational	–	–	–	2019/12/30	Not yet recruiting

PSC, pulmonary sarcomatoid carcinoma; ORR, objective response rate; PFS, progression-free survival; RR, response rate; OR, overall response.

respectively (162). Similarly, subgroup analysis indicated no statistically significant differences in ORR, DCR, PFS, or OS across treatment modalities (162).

Efficacy has also been demonstrated in patients treated with second-line therapy or beyond. A multicenter retrospective study by Domblides *et al.* included 37 patients with PSC treated with ICIs as second-line treatment (20 patients) or beyond (17 patients) who had received first-line platinum-based chemotherapy before immunotherapy. Of these patients, 32 patients received nivolumab, 3 received pembrolizumab, and 2 received atezolizumab (37). The ORR was 40.5%, the DCR was 64.8%, the median PFS was 4.89 months, and the OS was 12.7 months (37). The ORR of patients with PSC was twice as high as that of those with other types of NSCLC (40.5% *vs.* 20%) (37,163). Another similar study involving 49 patients who received pembrolizumab (40 patients), nivolumab (7 patients), or atezolizumab (2 patients), with 38 on second-line therapy, reported an ORR of 49.0%, a median PFS of 7.2 months, and a median OS of 22.2 months (164).

Regarding dual immunotherapy, a phase II study (NCT03022500) evaluated the efficacy and safety of durvalumab plus tremelimumab in recurrent or metastatic PSC (41). Out of 18 enrolled patients, 15 were analyzed for the primary endpoint. The ORR was 26.7%, and the median PFS and OS were 5.9 and 15.4 months, respectively (41).

Both first- and second-line immunotherapy and immune-combination therapy have demonstrated reliable efficacy in PSC. However, there have been reports of severe adverse reactions or rapid progression following immunotherapy in some cases (37,165), emphasizing the importance of comprehensive consideration in clinical decision-making. Most recent or ongoing clinical studies in PSC are focused on immunotherapy (*Table 2*).

Conclusions

The complexity of PSC as a highly malignant subgroup of NSCLC is compounded by its histologic subtypes and diverse cellular compositions. Although many studies (8,11-13,25-35) have confirmed the common origin of PSC's two components, *in vitro* and *in vivo* research has not sufficiently advanced to replicate this translational process. However, achieving this requires a comprehensive understanding of the cellular status of the sarcomatoid component, for which techniques such as single-cell RNA sequencing, spatial omics, or proteomics may be useful. PSC displays a substantially high degree of genetic mutation although the frequency and types of mutations vary across different ethnicities, indicating significant

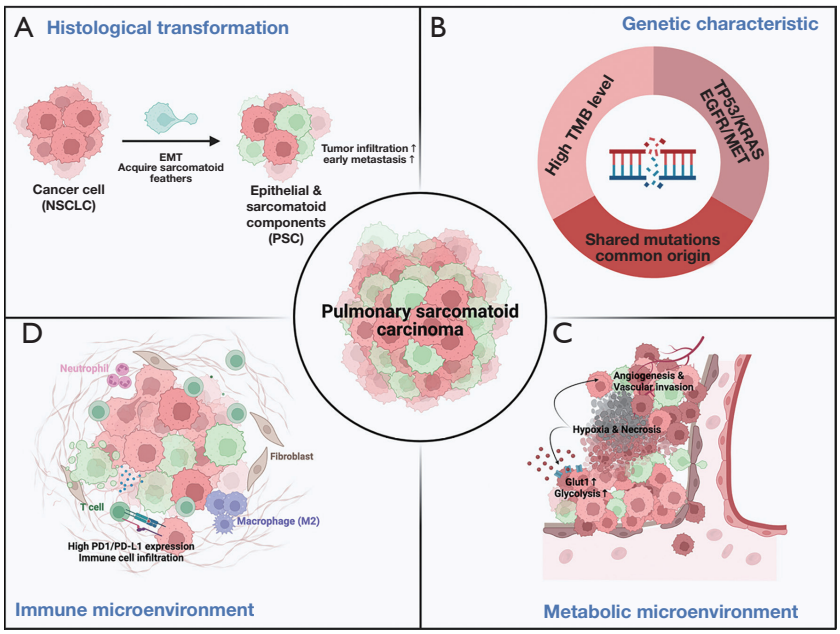

Figure 2 Biological characteristics of PSC. (Designed with BioRender). (A) Common origin of different components of PSC, in which EMT plays a key role. (B) PSC exhibits a high TMB. The most common mutations are *TP53*, *KRAS*, *EGFR*, and *MET*, with the majority of mutations being shared in epithelial and sarcomatoid components. (C) PSC has a high degree of hypoxia, which promotes glycolysis (Glut1 expression increased) and angiogenesis. (D) High levels of immune infiltration and checkpoint expression suggest that PSC is a "hot tumor". NSCLC, non-small cell lung cancer; EMT, epithelial mesenchymal transition; PSC, pulmonary sarcomatoid carcinoma; TMB, tumor mutational burden; *TP53*, tumor protein 53; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal to epithelial transition factor; Glut1, glucose transporter 1; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

heterogeneity among patients. Therefore, genetic testing is necessary for the precise treatment decision. High levels of hypoxia, glycolysis, and angiogenesis with vascular invasion might contribute to drug resistance and frequent metastasis in PSC, with this being potentially linked to the specific microenvironment of the sarcomatoid component. However, these correlations need to be validated by basic research. The high expression of immune checkpoints and the infiltration of immune cells suggest that PSC can be classified as a hot tumor with adaptive immune resistance. The various biological characteristics of PSC are summarized in *Figure 2*.

The unfavorable prognosis of PSC can be attributed to its resistance to chemotherapy and radiotherapy. A higher mutation frequency and immune infiltration suggest that targeted therapy and immunotherapy may be highly efficacious for PSC (*Figure 3*). Savolitinib is the only MET inhibitor that has been prospectively studied in patients with *MET* exon 14 skipping mutations. There are various opinions concerning the efficacy of inhibitors targeting other actionable mutation sites, necessitating systematic prospective clinical validation. The potential of antiangiogenic therapy in PSC appears promising, and clinical study indicate that antiangiogenic therapy combined with chemotherapy is significantly more effective than chemotherapy alone (111). Retrospective analyses of first- and second-line immunotherapies have yielded favorable outcomes, and dual immunotherapy trials have also shown promise, as have combination therapies. Various dual antibodies such as PD-1 plus VEGF or PD-L1 plus VEGF are also worth attempting in PSC.

To date, most of the literature in PSC consists of retrospective studies and case reports. Prospective clinical data and basic biological studies for PSC are limited. Multiple centers worldwide are engaging in prospective clinical studies evaluating a variety of treatment strategies for PSC (*Table 2*). Basic research in multiomics related to PSC should also be undertaken.

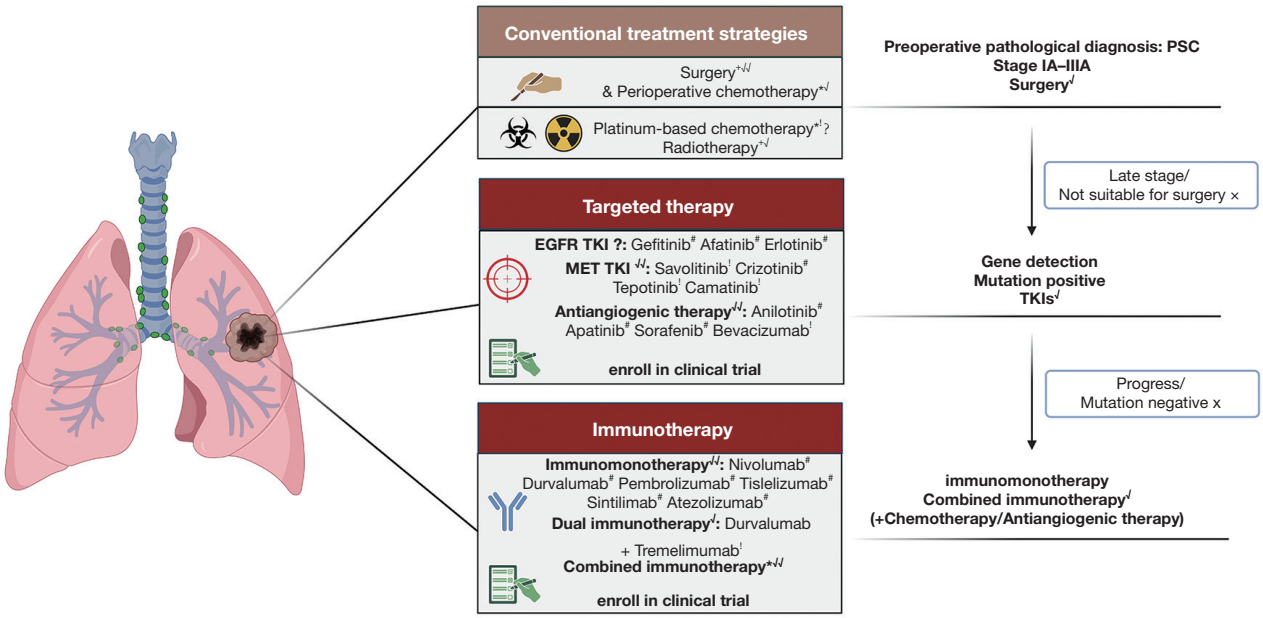

Figure 3 Therapeutic approaches in PSC. (Designed with BioRender). !, clinical trial; *, retrospective study; +, database analysis; #, case report. The symbols in the left box represent the efficiency of clinical treatment (√√, effective; √, likely effective; ?, controversial). The right side summarizes the clinical treatment strategies for PSC (National Comprehensive Cancer Network Guidelines, 2023) (166). PSC, pulmonary sarcomatoid carcinoma; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal to epithelial transition factor; TKI, tyrosine kinase inhibitor.

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Footnote

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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.

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