Journal of Cancer Research and Clinical Oncology (2025) 151:147
https://doi.org/10.1007/s00432-025-06203-z

REVIEW

Management strategies for primary lung carcinosarcoma: a case study and comprehensive literature review

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Received: 28 February 2025 / Accepted: 14 April 2025 / Published online: 22 April 2025

Abstract

Background Primary lung carcinosarcoma, characterized by the presence of both carcinoma and sarcoma components, is a rare soft tissue malignancy. Its pathogenesis remains incompletely elucidated, and it exhibits significant resistance to conventional therapeutic interventions, resulting in a dismal prognosis. Consequently, there is currently no established standard treatment protocol for lung carcinosarcoma, leading most clinicians to draw upon their experiences with other tumor types when formulating treatment strategies.

Case description A 56-year-old non-smoking male presented with a progressively enlarging mass in the right cervical region, The diagnosis of lung carcinosarcoma was definitively confirmed through CT-guided biopsy. First-line immunotherapy combined with targeted therapy was ineffective; second-line chemotherapy was effective, chest CT revealed the disappearance of enlarged lymph nodes in the retrosternal area and a significant reduction of pulmonary lesions, but showed signs of brain metastasis. the patient passed away at home on June 27th, 2023 due to sudden onset dyspnea accompanied by loss of consciousness.

Literature review A comprehensive literature search for lung carcinosarcoma was conducted across four databases, including PubMed/MEDLINE, Web of Science, Cochrane Library, and Embase, covering the period from 1968 to 2023. A total of 48 patients were included for analysis. Further survival analysis revealed a median survival time of 18 months; adjuvant therapy following surgery significantly improved survival compared to surgery alone and other treatment modalities.

Conclusion Lung carcinosarcoma is an exceptionally rare malignant neoplasm of the lung, and definitive treatment protocols remain elusive. The most effective strategy to enhance prognosis may still entail complete surgical resection of the lesions in conjunction with adjuvant therapy.

Novelty and impact

1.Lung carcinosarcoma is an exceptionally rare malignant neoplasm of the lung, and definitive treatment protocols remain elusive.
2.The most effective strategy to enhance prognosis may still entail complete surgical resection of the lesions in conjunction with adjuvant therapy.
3.Patients with lung carcinosarcoma should strive to undergo complete surgical resection of the lesions and receive adjuvant therapy

Keywords Lung carcinosarcoma · Carcinosarcoma · Lung cancer

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Extended author information available on the last page of the article

Introduction

Cancer is the leading cause of unnatural death in the global population (Ma et al. 2023). It results from uncontrolled cell proliferation, leading to destruction of normal cells and tissues at the original site and potential spread to other parts of the body (Srivastava et al. 2024). According to the histological origin, cancer is classified into three categories: carcinoma, sarcoma and carcinosarcoma. Carcinomas are the most common type of malignant tumors, originating in epithelial tissue (Francesco et al. 2014). The malignant tumors originating from mesenchymal tissue are collectively known as sarcomas. Sarcomas are mainly categorized into soft tissue sarcomas and osteosarcoma.

The tumours containing both carcinoma and sarcoma components are also referred to as carcinosarcomas (Alem and AlNoury 2014), which are malignant neoplasms characterized by the coexistence of malignant epithelial and mesenchymal elements. Carcinosarcomas exhibit high invasiveness, metastatic potential, and risk of recurrence (Salemis 2018). They can arise in various organs including the head and neck, digestive tract, genitourinary tract (kidneys, bladder, uterus) breast, and lungs (Colizza et al. 2022). Primary uterine carcinosarcoma is a rare and highly invasive tumor, accounting for less than 5% of all uterine tumors, with a 5-year survival rate of approximately 26-34%[7]. The incidence of primary liver carcinosarcoma is also exceedingly rare, characterized by high invasiveness and metastasis. Up to 2018, only 29 cases had been reported with an average survival time of 11.2 months (Li et al. 2018). Among all locations, primary lung carcinosarcoma is a very rare subtype of carcinosarcoma.

According to previous reports, the incidence of lung carcinosarcoma accounted for only 0.1 to 4.7% of all lung malignancies, and sarcomatoid cancer was also classified as a subtype of lung cancer sarcoma (Pelosi et al. 2010). Until 2015, the WHO classification identified lung carcinosarcoma as a distinct subtype of sarcomatoid cancer with poor cellular differentiation (Mengoli et al. 2018). The diagnosis of primary lung carcinosarcoma primarily relies on morphological features and immunohistochemical staining (Devi et al. 2019). In the reported cases, most patients were diagnosed with lung carcinosarcoma following biopsy and immunohistochemistry analysis of pathological tissues (Cen et al. 2020). A small number of patients were posthumously diagnosed with primary carcinosarcoma upon autopsy (Kitazawa et al. 2006). It is important to note that there is currently no established standard treatment for lung carcinosarcoma, and the majority of clinicians rely on their experience with other tumor types when making treatment decisions. Patients in the early stages typically choose to undergo for surgical resection of the tumor followed by adjuvant radiotherapy or chemotherapy (Panagiotopoulos et al. 2016). Although the effectiveness of radiotherapy and chemotherapy in treating lung carcinosarcoma is controversial, these modalities have emerged as primary treatment options for patients with unresectable tumors. While some studies have shown that radiotherapy and chemotherapy can provide temporary relief from tumors, there are also reports indicating their ineffective (Liang et al. 2022; Mekheal et al. 2022).

Here, we present a 56-year-old non-smoking male with pulmonary carcinosarcoma, who failed initial treatment with Camrelizumab in combination with Anlotinib as first-line therapy despite positive PD-L1 expression by IHC testing. However, although the second-line combination chemotherapy regimen, comprising Camrelizumab, Anlotinib, Cyclophosphamide, Epirubicin, and Carboplatin, demonstrated efficacy in treating lung lesions, the patient unfortunately developed brain metastases and succumbed to the disease. In addition, the data of 48 patients diagnosed with primary lung carcinosarcoma between 1968 and 2023 has been collected and further survival analysis, which can enhance the clinicians' understanding of the disease and formulate a optimal treatment plan.

Case presentation

A 56-year-old non-smoking male presented at The Third People's Hospital of Yunnan Province on January 28, 2023 with a progressively enlarging mass in the right neck, seeking medical attention. The patient had an unremarkable medical history with no evidence of tumors or prior radiation exposure, and no notable family history. Prior to admission, he was in excellent health and maintained a typical lifestyle. The cervico-thoracic CT imaging revealed multiple nodular shadows of various sizes within the right cervical region posterior to the sternocleidomastoid muscle and adjacent to the carotid artery sheath, which partially fused. The largest measured approximately 3.8 cm × 2.6 cm with indistinct margins and uneven ring-shaped enhancement (Fig. 1Aa-b). Compression of the right parapharyngeal soft tissue and right jugular vein was evident (Fig. 1Aa). Furthermore, enlarged lymph nodes with partial fusion were identified in the mediastinum (Fig. 1Ac-d), a round-like mass measuring approximately 9.8 cm × 8.0 cm in size, with well-defined borders, uneven density, and heterogeneous enhancement, was identified in the extra-basal segment of the left lower lung lobe (Fig. 1Ae). The presence of pulmonary malignancy with cervical and mediastinal lymph node metastasis was suspected based on CT examination. No significant abnormalities were observed on CT scans of the head and abdomen, as well as during the hematological examination.

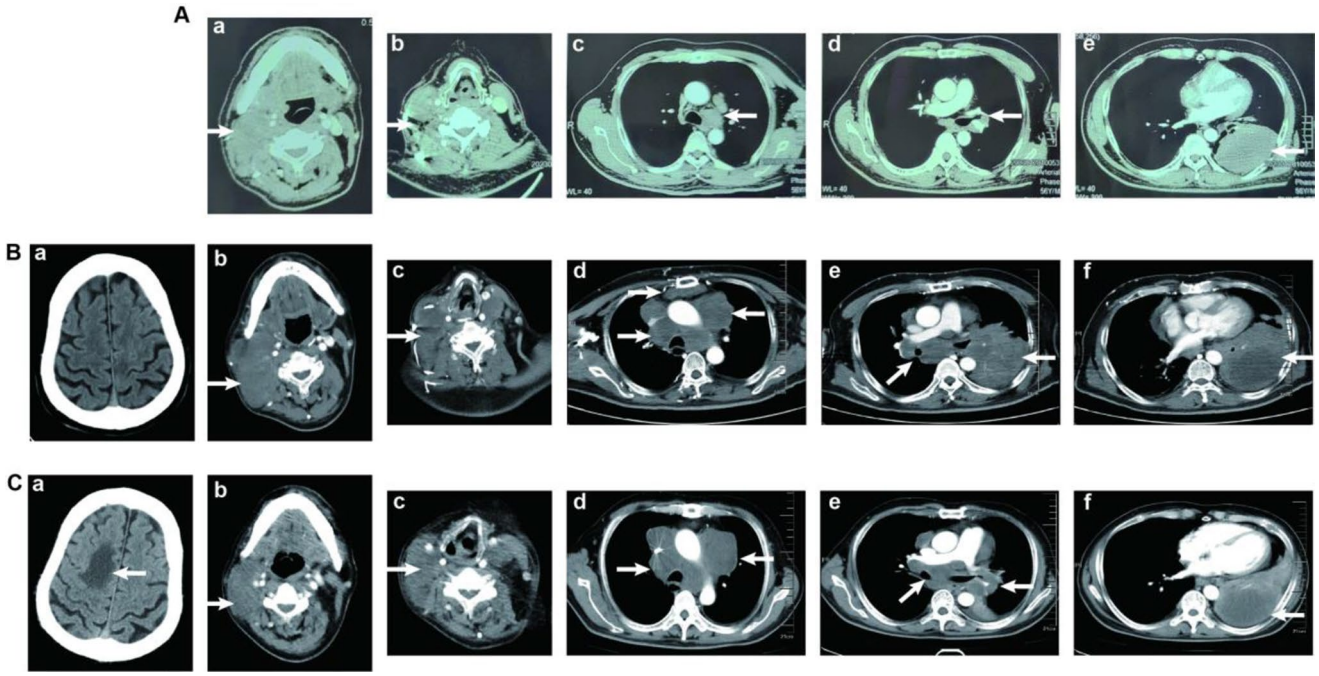

Fig. 1 CT scans of the neck and chest showed the lesion. **A** is the mass of the neck and left lower lobe of the lung before treatment; **B** is the brain, neck and chest images following two cycles of Camrelizumab and Anlotinib; **C** is the images following two cycles of Camrelizumab and Anlotinib plus chemotherapy

To determine the pathological type of the patient's tumor, CT-guided puncture biopsy was performed on the mass in the left inferior lobe of the lung. Subsequently, the puncture tissues underwent pathological diagnosis and genetic detection. Immunohistochemistry showed that the positive rate of the Ki-67 index was 80%, the positive of CKpan, Vimentin, CK7, CK19, EMA, CK8/18, EGFR, ALK, MLH1, MSH6, PMS2, MSH2 and TDT. However, S-100, LCA, p40, CK5/6, p63, TTF-1, Napsin A, CD56, CGA, Syn, CD117, Her-2, Villin, CK20, CD1a, MUC5AC, Bcl-2, CR and MC were negative. After integrating the findings from HE staining and immunohistochemistry, the diagnosis of lung carcinosarcoma was conclusively established. Immunohistochemistry revealed that the positive rate of PD-L1 was 80% in tumor proportion score (TPS) and 90 in combined positive score (CPS) (Fig. 2). Next-generation sequencing (NGS) revealed a tumor mutational burden (TMB) of 7.9 mutations per megabase (mut/Mb) and microsatellite stability (MSS). Additionally, a KRAS mutation (exon 2: c.G35A: p.G12D) was detected at a frequency of 15.13%, and a P53 mutation (exon 5: c.C535:p.H179Y) was identified at a frequency of 14.13%.

In the initial treatment, the patient received 2 cycles of Camrelizumab (200 mg administered every 21 days) in combination with Anlotinib (12 mg orally taken daily for 14 consecutive days followed by a 7-day break). However, the initial chemotherapy regimen "Camrelizumab + Anlotinib" was ineffective in reducing the neck mass, leading the patient to seek treatment at the First Affiliated Hospital of Kunming Medical University due to continued tumor enlargement and progressive symptoms of hoarseness, increased oral secretions, difficulty breathing, and inability to lie flat. The cervical and chest CT revealed a significant increase in size of the cervical lymph node, mediastinal lymph node, and lung lesions compared to previous scans (Fig. 1Bb-f). The lung lesions measured approximately 12.3 cm × 9.4 cm × 10.4 cm and have coalesced with the mediastinal lesions, resulting in compression of the superior vena cava (Fig. 1Bf). Subsequently, Tumor-associated antigen testing revealed elevated levels of carbohydrate antigen 125 (CA125) at 71.65 IU/ml and neuron-specific enolase (NSE) at 244.20 ng/ml. A comprehensive thyroid function assessment demonstrated free triiodothyronine (FT3) at 1.84 pg/ml, free thyroxine (FT4) at 5.04 pg/ml, thyroid-stimulating hormone (TSH) at 38.80 uIU/ml, thyroglobulin (TG) < 0.02 ng/ml, thyroid microsomal protein antibody (TMAb) > 1000%, and thyroglobulin antibody (TGAb) > 2800%. The CT scans of the head and abdomen, along with other laboratory parameters, showed no significant abnormalities.

After a thorough assessment, the patient underwent two cycles of the combination chemotherapy regimen consisting of Camrelizumab (200 mg administered every 21 days), Anlotinib (12 mg orally taken daily for 14 consecutive days followed by a 7-day break), Cyclophosphamide (600 mg per square meter of body surface area, administered every 21 days), Epirubicin (60 mg per square meter of body

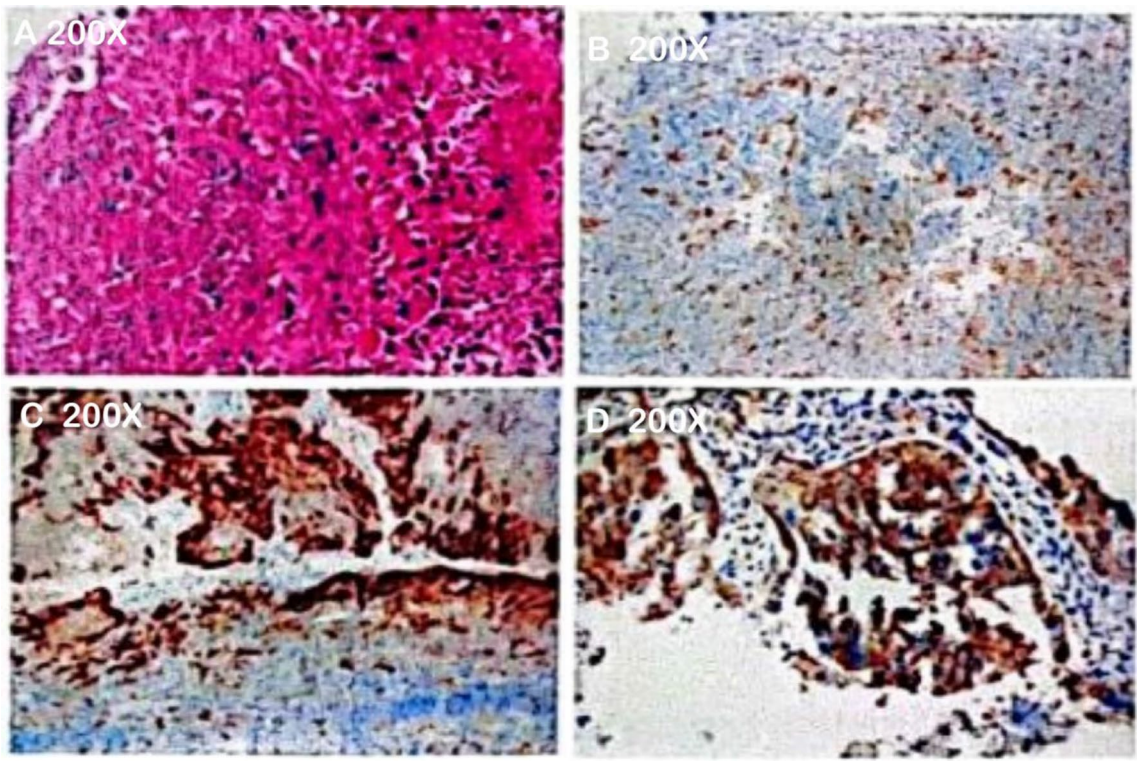

Fig. 2 Pathological diagnosis and the immunohistochemistry (IHC) results of PD-L1. **A**: The result of HE stained section of pathological tissue. **B**: The negative control in the IHC results for PD-L1. **C**: The positive control in the IHC results for PD-L1. **D**: The IHC results of PD-L1 in this case

surface area, administered every 21 days), and Carboplatin (AUC = 5, administered every 21 days). Subsequently, the patient experienced grade 1 adverse effects including nausea, vomiting, dysphagia and neutropenia. The side effects promptly resolved with symptomatic supportive care. Following two cycles of the combination chemotherapy regimen, a neck CT showed a reduction in the size of multiple enlarged lymph nodes in the neck and infraclavicular fossa (Fig. 1Cb-c). Additionally, chest CT revealed the disappearance of enlarged lymph nodes in the retrosternal area and a significant reduction of pulmonary lesions (Fig. 1Cd-f). However, brain CT performed 70 days after the initiation of the first cycle combination chemotherapy revealed a patchy iso-hyperdense shadow in the right frontal lobe with extensive surrounding edema, consistent with brain metastasis of lung cancer sarcoma given the patient's medical history (Fig. 1Ca). The tumor-associated antigen testing revealed an elevated level of CA125 at 155.10 IU/ml and n a reduction in NSE to 171.50 ng/ml. Thyroid function evaluation showed TSH at 18.81 uIU/ml, thyroglobulin (TG) at 1.03 ng/ml, thyroid microsomal antibody (aTG) at > 1000%, and thyroglobulin antibody (aTG) at > 2800%. The patient was discharged following the completion of a third cycle of combination chemotherapy regimen. Subsequently, the patient's condition remained stable. Unfortunately, the patient died at home on June 27, 2023 due to sudden dyspnea and loss of consciousness while awaiting admission for further treatment. The process of clinical diagnosis and treatment for this patient is shown in Figure 3.

Literature review

Four databases, including PubMed/MEDLINE, Web of Science, Cochrane library, and Embase, were searched using the keywords "lung carcinosarcoma" and "pulmonary carcinosarcoma" to conduct a comprehensive literature search. Due to the low incidence of lung carcinosarcoma, previous studies have classified sarcomatoid carcinoma as a subtype of lung carcinosarcoma for analysis. However, after reclassification by WHO in 2015, lung carcinosarcoma was then categorized as a subtype of sarcomatoid carcinoma. Therefore, in our study, we excluded studies that included sarcomatoid carcinoma and only included cases with a definitive pathological diagnosis of lung carcinosarcoma for further analysis. The data of 48 patients (including this case) diagnosed with primary lung carcinosarcoma between 1968 and 2023 has been collected and presented in Table 1.

Among the 48 cases, 45 individuals (94%) were aged over 40 years (ranging from 25 to 90 years), with 30 cases (62%) having a history of smoking. The male-to-female ratio was 3.8:1, comprising of 38 male and 10 female patients. Notably, 39 cases (81%) underwent surgical intervention, while

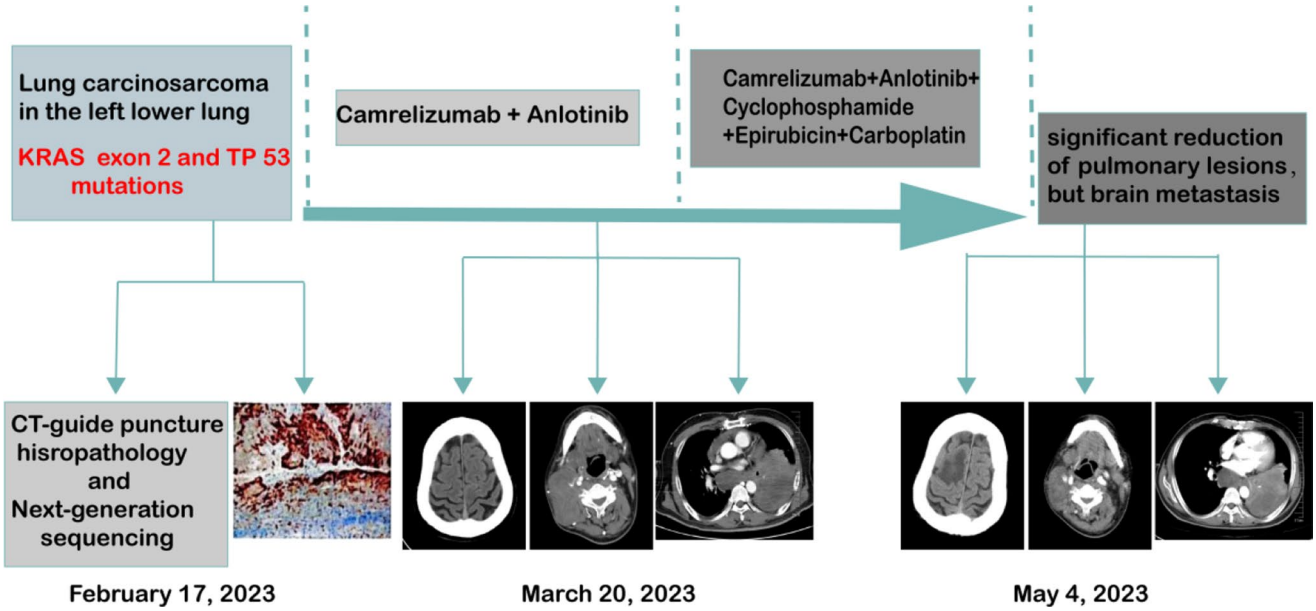

Fig. 3 A summary of the treatment strategy employed in this patient

18 received chemotherapy, 6 underwent radiotherapy, 3 cases underwent immune therapy, and 4 cases accepted the targeted therapy (including antiangiogenic agents); in addition, 2 cases received support treatment.

In our study involving 48 patients, we observed that the epithelial component predominantly consisted of squamous cell carcinoma, followed by adenocarcinoma. The sarcoma component primarily consisted of osteochondroma, and also included osteosarcoma and rhabdomyosarcoma. This discovery contrasts with the findings of Koss et al. (Koss et al. 1999), who identified rhabdomyosarcoma as the most common sarcoma component. The tumors are frequently identified by the presence of a large mass(3–15 cm), often accompanied by areas of necrotic tissue. Out of the 48 patients, three were found to have gene mutations. Specifically, two patients exhibited EGFR gene mutations, including one with EGFR exon 19Del and TP53 mutations (Wang et al. 2023), and another with EGFR gene mutation and mesenchymal lymphoma kinase (ALK) gene rearrangement (Toyokawa et al. 2013). Our reported patient was found to have concurrent mutations in the KRAS gene and TP53, as well as high expression of PD-L1.

Further survival analysis of 48 patients showed that the survival period ranged from 1 to 35 months, with 22 deaths reported at the time of follow-up, and the median survival time was 18 months (range: 1–35 months)(Fig. 4A). Kaplan-Meier survival analysis showed that adjuvant therapy after surgery aignificant improve the survival than surgery alone and other treatments ($P=0.0055$) (Fig. 4B). However, no statistically significant differences were observed in tumor size (Fig. 4C), lymph node metastasis (Fig. 4D), distant metastasis (Fig. 4E), stage (Fig. 4F), bronchial involvement (Fig. 2G), smoking (Fig. 4H), age (Fig. 4I), and gender (Fig. 4J) ($P>0.05$).

Discussion

Carcinosarcoma is a malignant tumor characterized by the coexistence of carcinoma and sarcoma components, primarily originating from aberrant cells in bone or soft tissue (Almond et al. 2017). It demonstrates invasive behavior, often infiltrating surrounding tissues or organs, with a predisposition to recurrence and metastasis, and associated with a poor prognosis (Alem and AlNoury 2014). The carcinosarcoma can present in various anatomical locations, including the head and neck, digestive tract, genitourinary tract (such as kidneys, bladder, uterus), mammary glands, and lungs (Devi et al. 2019). Symptoms may vary depending on the size and location of the tumor. Prognostic factors include tumor size, presence of distant metastases, and the proportion of sarcomas (Gleason et al. 2017).

According to previous reports, many clinicians mistakenly conflate carcinosarcoma and sarcomatoid carcinoma as the same disease, despite their fundamentally different origins, with carcinosarcoma consisting of both epithelial and mesenchymal components (Amin et al. 2023). The carcinosarcoma of the lung is a rare subtype of non-small cell lung cancer characterized by spindle cells and/or giant cells. The incidence of lung carcinosarcoma accounts for only 0.1 to 4.7% of all lung malignancies, and sarcomatoid cancer has long been classified as a subtype of lung carcinosarcoma

Table 1 Literature review of primary lung carcinosarcoma

Authors, year	Nation	Sex/ Age (years)	History of smoking	Treatment	Survival time (months)/Prognosis	TNM stage
Jenkins, B. J et al. 1968	America	M/81	Unknown	STx	1/dead	/
Vidal Losada et al. 2010	Spain	M/75	+	Surgery + STx	7/dead	T2N2M0
Wang, Hongming et al. 2023	China	M/56	+	Surgery + CTTx	13/alive	T2aN0M0
Zehani et al. 2013	Tunis	M/71	+	Surgery + CTx	4/dead	T3N1M0
	Tunis	M/47	+	Surgery + CTx	3/dead	T4N1M0
	Tunis	F/65	-	Surgery	8/dead	T3N2M0
Devi et al. 2019	America	F/71	-	Surgery + CTx	6/alive	T4N0
Grahmann et al. 1993	Germany	M/59	+	Surgery	33/alive	T2N1M0
	Germany	M/65	+	Surgery	35/alive	/
	Germany	M/56	-	Surgery	7/dead	TxNxM1
This case	China	M/57	-	CIT + TTx	4/dead	T4N3M1
Sökücü et al. 2012	Turkey	M/63	+	Surgery	10/dead	T3N0M1
	Turkey	M/66	+	Surgery + CTx	9/dead	T3N1M0
	Turkey	M/54	+	Surgery + CTx	25/alive	T3N1M0
	Turkey	M/53	+	Surgery	5/dead	T3N0M0
	Turkey	M/55	+	Surgery	6/alive	T2aN0M0
	Turkey	M/56	+	Surgery	3/dead	T2bN0M0
Nakamura et al. 2019	Japan	M/42	+	Surgery + CRT	/alive	/
Mekheal et al. 2022	America	M/62	+	Surgery	6/dead	T4N0M1a
Schaefer et al. 2012	Germany	M/58	+	Surgery	30/alive	T3N0Mx
Ciralik et al. 2012	Turkey	M/57	-	Surgery	4/dead	/
Kim et al. 2002	Korea	M/66	+	Surgery	6/alive	T2N0M0
Lin, C.-T.et.al 2010	China	M/25	-	Surgery + CRT	12/alive	/
Haraguchi et al. 1999	Japan	M/68	+	Surgery	32/alive	/
Chuang et al. 2012	China	M/31	-	Surgery	12/alive	/
Kanzaki et al. 2012	Japan	M/39	+	Surgery	6/alive	/
Ishibashi, N. et al 2023	Japan	F/73	-	Surgery + CTx	16/alive	T2aN0M0
Kitazawa et al. 2006	Japan	M/57	+	CTx	6/dead	/
Akbulut et al. 2009	Turkey	F/74	Unknown	Surgery + CTx	3/alive	/
Misthos et al. 2013	Greece	M/70	Unknown	Surgery + CTx	12/alive	/
Koba et al. 2018	Japan	F/73	-	Surgery	/alive	T2aN3M0
Toyokawa et al. 2013	Japan	F/61	-	Surgery + RTx	1/alive	/
Spagnoli et al. 2022	Italy	M/54	+	Surgery + CIT	36/alive	T4N2M0
Zhang, Zhe et al. 2017	China	M/64	-	ITx	/alive	/
Tanz et al. 2017	Morocco	M/46	+	CTx	4dead	TxNxM1
Gleason et al. 2017	America	F/76	+	RTx	1/dead	TxNxM1
Sato et al. 2010	Japan	M/65	+	Surgery + CRT	7/alive	T2N0M0
Tanimoto et al. 2018	Japan	M/65	-	Surgery + CTTx	6/alive	T3N1M1
Liang, Long et al. 2022	China	M/88	+	TTx	9/alive	T4N0M0
Vohra et al. 2014	India	M/90	+	NO	/	TxNxM1
Kanehisa et al. 1993	Japan	M/77	Unknown	Surgery	9/dead	TxNxM1
Thomas et al. 2012	America	F/63	+	CTx	1/dead	TxNxM1
Takashima et al. 2019	Japan	M/80	Unknown	Surgery	4/alive	TxNxM1
Sakane et al. 2018	Japan	M/65	+	Surgery + RTx	10/dead	T2aN2M0
	Japan	M/62	+	Surgery	1/dead	T3N0M0
	Japan	F/69	+	Surgery	1/dead	T3N0M0
	Japan	M/71	+	Surgery	14/dead	T4N3M0
	Japan	F/65	-	Surgery + CTx	24/dead	T3N2M0

M: Male, F: Female, Yes: +, No: -, CRT: Chemo-RadiationTherapy, CTx: Chemotherapy, RTx: RadiationTherapy, ITx: Immunotherapy, CIT: Chemotherapy + Immunotherapy, STx: Supportivetherapy, PTx: Palliative therapy, TTx: Targeted Therapy, CTTx: Chemotherapy + Targeted Therapy

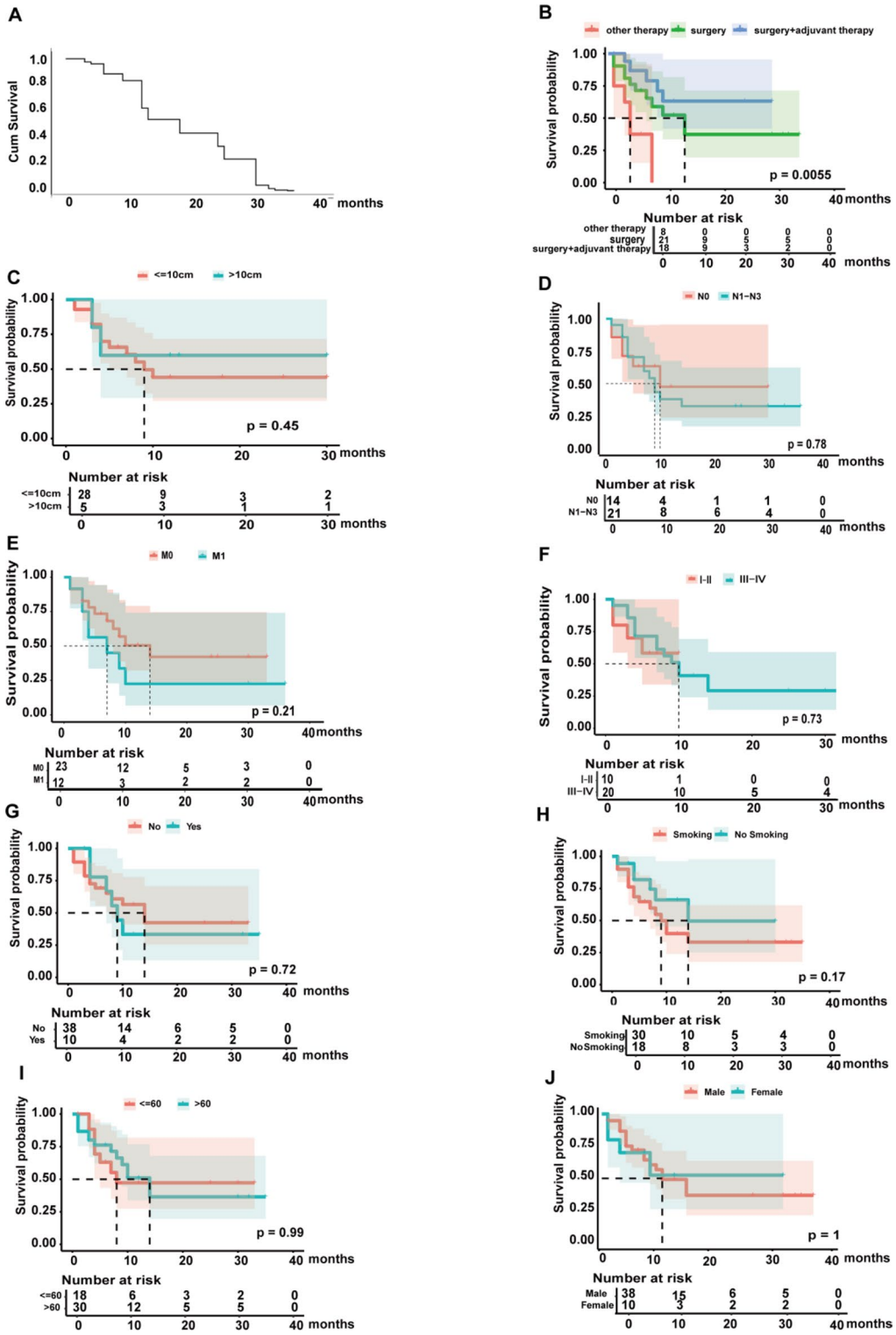

Fig. 4 Kaplan-Meier method was used to calculate the survival rate of patients with lung carcinosarcoma. **A**: Overall survival rate, **B**: treatment methods, **C**: tumor size, **D**: lymph node metastasis, **E**: distant metastasis, **F**: tumor staging, **G**: bronchial involvement, **H**: smoking, **I**: age, and **J**: gender. P values were estimated by log-rank test, and were considered significant at $P<0.05$

(Pelosi et al. 2010). The WHO classified sarcomatoid carcinoma of the lung into five subtypes until 2015: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, sarcomatoid carcinoma, and pneumoblastoma. Carcinosarcoma is a distinct subtype of sarcomatoid carcinoma with poor cellular differentiation (Roesel et al. 2017), constituting only 4% of sarcomatoid carcinomas and sharing similar epidemiological characteristics (Vieira et al. 2012).

Lung carcinosarcoma is a specific high-grade tumour consisting of both epithelial and mesenchymal cells, characterized by carcinoma of the lung parenchyma and mesenchymal sarcomatoid changes (Sökücü et al. 2012). The disease predominantly affects middle-aged smokers and older men, particularly those between the ages of 40 and 70 who smoke (Vidal Losada et al. 2010). The median age at diagnosis typically falls around 65 years old (Panagiotopoulos et al. 2016). After analyzing the data of 48 patients diagnosed with primary lung carcinosarcoma between 1968 and 2023, we discovered that 62.5% (30/48) of the patients were smokers, with a median age of 65 years. The gold standard for diagnosis is immunophenotyping and morphology (Dong et al. 2022). Pathological examination typically reveals poorly differentiated spindle cells and pleomorphic cells, consisting of both epithelial and mesenchymal components. Some studies recommend that the specific type and proportion of epithelial and stromal components should be determined during pathological diagnosis (Roesel et al. 2017).

Studies have consistently demonstrated a poor prognosis for lung carcinosarcoma, with a median survival period of approximately 10 months and a 5-year survival rate of only 6% post-diagnosis[25], with direct correlation to tumor size. It is noteworthy that there is currently no standard treatment for lung carcinosarcoma, and the majority of clinicians base their treatment choices on experience, cancer and sarcoma composition, and their proportion (Devi et al. 2019). By consensus, complete resection is the essential treatment for the disease without metastasis. However, the role of adjuvant chemotherapy for PCS patients remains unclear, and previous reports have indicated poor response to chemotherapy in advanced PCS. Additionally, attempts by medical oncologists to employ sarcoma regimens such as anthracycline and/or ifosfamide-based chemotherapy, or combination regimens targeting both the carcinomaous and sarcomatoid components, whether neoadjuvant or adjuvant including platinum-based combinations and doxorubicin- and/or ifosfamide-based combinations, have all failed to improve patients' survival (Yang et al. 2017). As a result, there have been few interventional studies on chemo- and/or radiotherapy against metastatic/recurrent PCS until now.

Targeted therapies directed at mutations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) fusion gene, or ROS1 fusion gene play a crucial role in the treatment of non-small cell lung cancer (NSCLC) (Ettinger et al. 2021). The studies on genetic mutations in lung carcinosarcoma have reported inconsistent findings, with the majority of them failing to differentiate between rare lung tumors such as lung cancer sarcoma and sarcomatoid carcinoma. Furthermore, most patients with genetic mutations exhibit components of lung adenocarcinoma, suggesting a stronger association between genetic mutations and adenocarcinoma components than with other rare components (Pelosi et al. 2012; Italiano et al. 2009; Jiang et al. 2012). Therefore, these findings may imply that it represents a distinct subtype of lung cancer and further investigation is required to elucidate the potential role of molecular targeted therapy in treating this particular entity.

Despite the widespread use of PD-1/PD-L1 inhibitors in non-small cell lung cancer treatment, only 1 cases have been reported in carcinosarcoma (Zhang et al. 2017). Zhang Zhe et al. described a case of pulmonary carcinosarcoma, with the positive expression of PD-L1, obtained a significant benefit from Nivolumab treatment in a 64-year-old Chinese man, with the tumor were rapidly decreased and obtained partial remission (PR) after two cycles of Nivolumab, and the lesions present a good trend to decrease in the follow-up treatment (Zhang et al. 2017). Nevertheless, our case elicited a distinct response. A 56-year-old non-smoking male with pulmonary carcinosarcoma, who failed initial treatment with Camrelizumab in combination with Anlotinib as first-line therapy despite positive PD-L1 expression by IHC testing. However, although the second-line combination chemotherapy regimen, comprising Camrelizumab, Anlotinib, Cyclophosphamide, Epirubicin, and Carboplatin, demonstrated efficacy in treating lung lesions, the patient unfortunately developed brain metastases and succumbed to the disease. It reminde that the effectiveness of the anti PD-L1 therapy treatment for lung carcinosarcoma remains controversial, needs further research to confirm.

This study reports the treatment responses and prognostic characteristics of three cases of primary pulmonary carcinosarcoma harboring distinct driver gene mutations. The first case exhibited EGFR exon 19 deletion combined with ALK rearrangement (Toyokawa et al. 2013), the second case showed EGFR exon 19 deletion with TP53 mutation (Wang et al. 2023), and the third case demonstrated KRAS G12D and TP53 co-mutation. Notably, the patient with EGFR/TP53 co-mutation exhibit components of lung adenocarcinoma and exhibited significant and durable treatment responses to both osimertinib monotherapy and combination therapy with chemotherapy (pemetrexed + carboplatin). In contrast, the patient with KRAS/TP53 mutation, after failing first-line immunotherapy combined with targeted therapy, still achieved marked tumor regression

with second-line chemotherapy. These findings suggest that although pulmonary carcinosarcoma generally has a poor prognosis, specific molecular subtypes may demonstrate higher sensitivity to targeted therapy or chemotherapy, thereby potentially improving clinical outcomes. Furthermore, the observations from this case series support the implementation of comprehensive molecular profiling in pulmonary carcinosarcoma to guide personalized treatment strategies.

Moreover, pulmonary carcinosarcoma can be accompanied by various paraneoplastic syndromes, which further compromise patients' quality of life. In this study, a 75-year-old male patient presented with migratory polyarthritis, mixed motor neuropathy, and pseudomembranous colitis Notably, his arthritic symptoms completely resolved following tumor resection, while the neurological deficits persisted. This clinical course aligns with the hallmark features of paraneoplastic syndromes, wherein some manifestations may improve with tumor burden reduction while certain neurological impairments often remain irreversible. Although current literature contains limited reports on paraneoplastic syndromes associated with pulmonary carcinosarcoma, their multisystem involvement warrants clinical attention. Future studies should further investigate potential correlations between driver gene mutations and the development of paraneoplastic syndromes to optimize comprehensive management strategies for these patients.

This study included five patients with primary pulmonary carcinosarcoma and brain metastases. In one case, pazopanib treatment resulted in a 60% reduction in pulmonary lesions, while brain metastases continued to progress (Tanimoto et al. 2018). Another patient showed significant response to second-line chemotherapy in pulmonary lesions but no efficacy against brain metastases. These clinical observations suggest that current treatment strategies have limited efficacy in controlling brain metastases of pulmonary carcinosarcoma, highlighting the urgent need to develop novel targeted agents capable of effectively penetrating the blood-brain barrier to improve outcomes in these patients. These findings underscore an important direction for future research—focusing on the exploration of therapeutic agents with optimal blood-brain barrier permeability.

Our survival analysis of 48 patients showed that adjuvant therapy after surgery aignificant improve the survival than surgery alone and other treatments. This suggests that patients with lung carcinosarcoma should strive to undergo complete surgical resection of the lesions and receive adjuvant therapy, as this may currently be the only approach to improve the prognosis.This study identified a relatively higher number of pulmonary carcinosarcoma cases from Japan and Turkey. However, there is currently insufficient evidence to confirm a distinct geographic clustering in the incidence of this disease. To further investigate potential contributing factors, additional case data collection and in-depth epidemiological and molecular analyses are required.

In summary, lung carcinosarcoma represents an exceedingly rare malignant neoplasm of the lung, currently, the etiology and pathogenesis of this condition remain unclear, and there is a lack of definitive treatment protocols. Given the poor prognosis of lung carcinosarcoma, it is imperative to accumulate additional cases and expand sample sizes for systematic analysis of lung carcinosarcoma. The optimal approach to improve the prognosis may still involve complete surgical resection of the lesions combined with adjuvant therapy.

Acknowledgements Not applicable.

Author contributions ZW and YZ were involved in the identification and selection of patient cases and drafted the manuscript. QF and XZ reviewed and edited the manuscript. HJ, CL, FZ and QF were involved in the patient's clinical management. YZ and QF were involved in the identification, selection and management of patient cases, and reviewed and edited the manuscript. XZ and QF confirm the authenticity of all the raw data. All authors contributed to the article and read and approved the final version.

Funding This present study was supported by the Applied Basic Science Research Foundation of Yunnan Province (grant no. 202201AT070294), the Yunnan Revitalization Talent Support Program (grant no. RLQB20220014) and the 535 Talent Project of the First Affiliated Hospital of Kunming Medical University (grant no. 2023535D17).

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Informed consent Written informed consent was obtained from the patient 's family for the publication of the case report and all accompanying images.

Competing interests The authors declare no competing interests.

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