CANCER DIAGNOSIS & PROGNOSIS *5*: 363-369 (2025)
doi: 10.21873/cdp.10448

Multicenter Retrospective Analysis of Pulmonary Sarcomatoid Carcinoma Clinically Diagnosed Using Small Biopsy Specimens

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Abstract

Background/Aim: Pulmonary sarcomatoid carcinoma is a rare disease known for its aggressiveness, with numerous studies evaluating the efficacy of various therapeutic approaches. However, pulmonary sarcomatoid carcinoma is histologically defined according to WHO classification based on surgical specimens, whereas in clinical practice, most cases of advanced lung cancer are diagnosed based on small biopsy specimens. This retrospective study aimed to present the clinical course of patients diagnosed with pulmonary sarcomatoid carcinoma based on small biopsy specimens.

Patients and Methods: Data of patients who were diagnosed with pulmonary sarcomatoid carcinoma based on small biopsy specimens and treated with platinum-doublet chemotherapy and/or an immune checkpoint inhibitor-containing regimen between 2005 and 2022 were analyzed.

Results: Data from 12 patients were analyzed, including five patients treated with platinum-doublet chemotherapy and 11 patients treated with an immune checkpoint inhibitor-containing regimen. The median progression-free survival among the five patients treated with platinum-doublet chemotherapy was 1.5 months [95% confidence interval (CI)=0.7-4.1]. Of these, four patients subsequently received immune checkpoint inhibitor-containing therapy. The median overall survival from the initiation of platinum-doublet chemotherapy in these five patients was 14.7 months (95%CI=1.2-16.2). In contrast, 11 patients treated with immune checkpoint inhibitor therapy showed a median progression-free survival and overall survival of 8.9 months [95%CI=0.3-not estimated (NE)] and 10.8 months (95%CI=1.0-NE), respectively.

continued

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Received February 20, 2025 | Revised March 11, 2025 | Accepted March 12, 2025

Conclusion: Pulmonary sarcomatoid carcinoma diagnosed based on small biopsy specimens is refractory to platinum-doublet chemotherapy, and immune checkpoint inhibitor therapy may improve the prognosis.

Keywords: Small biopsy specimens, pulmonary sarcomatoid carcinoma, diagnosis, prognosis.

Introduction

Lung cancer is one of the leading causes of death worldwide (1). Among the various types of lung cancer, pulmonary sarcomatoid carcinoma has long attracted interest due to its rarity and aggressiveness. Several studies have reported poor outcomes in patients with pulmonary sarcomatoid carcinoma treated with chemotherapy. The median survival time after the initiation of the treatment with chemotherapy was reported to be 5–8 months (2-4). However, recent reports have suggested that immune checkpoint inhibitor (ICI) therapy improves the prognosis of patients with pulmonary sarcomatoid carcinoma, showing that the median overall survival (OS) was over one year in patients treated with ICI therapy (5-7).

One of the clinical issues is the validity of histological diagnosis. Sarcomatoid carcinoma is histologically defined based on the findings of surgical specimens, following the WHO classification. The 2015 WHO classification first provided the criteria for lung cancer diagnosis in small biopsies, and lung cancer with sarcomatoid components diagnosed using small specimens is defined as "non-small cell carcinoma with spindle cell and/or giant cell carcinoma" (8). However, in clinical practice, most cases of advanced lung cancer are diagnosed based on small biopsy specimens, which is the case for advanced pulmonary sarcomatoid carcinoma. Notably, it remains unclear whether the clinical diagnosis based on small biopsy specimens is identical to that based on surgical specimens.

We conducted this retrospective study to provide the characteristics and clinical course of patients with pulmonary sarcomatoid carcinoma diagnosed based on small biopsy specimens.

Patients and Methods

Patient selection. We established a database of patients with pulmonary sarcomatoid carcinoma who were diagnosed at Toyama University Hospital, Toyama Prefectural Central Hospital, or Toyama Red Cross Hospital between 2005 and 2022. Both patients in whom the diagnosis was confirmed using histopathological examination of surgical or autopsy specimens and patients who were clinically diagnosed as having pulmonary sarcomatoid carcinoma by attending physicians using small biopsy specimens were included (7, 9). In the present study, data of patients with sarcomatoid carcinoma clinically diagnosed using small biopsy specimens were extracted from the database and retrospectively analyzed. The following inclusion criteria were considered: 1) patients who were clinically diagnosed with pulmonary sarcomatoid carcinoma using small biopsy specimens; 2) patients with pulmonary sarcomatoid carcinoma who were treated with platinum-doublet chemotherapy and/or ICI-containing regimens (hereafter, ICI therapy).

The present study was approved by the Ethics Committee of the University of Toyama (approval number: R2020099) and conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan). Informed consent was waived due to the retrospective nature and noninvasiveness of the study, and the study was initiated after disclosing study information to the study participants.

Statistical analysis. The study endpoints were progression-free survival (PFS) and OS following the initiation of platinum-doublet chemotherapy or ICI therapy. PFS was calculated from the day of treatment initiation until the

Table I. *Patient characteristics and history of platinum doublet chemotherapy and immune checkpoint inhibitor therapy in 12 patients.*

Patient number	Sex	Smoking status	Biopsy procedure	Driver mutation	PD-L1 TPS (%)	Platinum doublet chemotherapy	Immune checkpoint inhibitor therapy
1	Male	Yes	TBB	Negative/unknown	Unknown	Received	Received
2	Male	Yes	Needle biopsy	Negative/unknown	Unknown	Received	Received
3	Male	Yes	Needle biopsy	Negative/unknown	40%	Received	Received
4	Male	Yes	Needle biopsy	Negative/unknown	Unknown	Received	
5	Male	Yes	Needle biopsy	Negative/unknown	40%	Received	Received
6	Male	Yes	TBB	MET	70%		Received
7	Female	Yes	TBB	Negative/unknown	70%		Received
8	Male	Yes	TBB	Negative/unknown	5%		Received
9	Male	Yes	TBB	Negative/unknown	Negative		Received
10	Male	Yes	Needle biopsy	Negative/unknown	80%		Received
11	Male	Yes	Needle biopsy	Negative/unknown	10%		Received
12	Male	Yes	Needle biopsy	Negative/unknown	Unknown		Received

PD-L1: Programmed death ligand-1; TBB: transbronchial biopsy; TPS: tumor proportion score.

Table II. *Background and clinical course of patients with pulmonary sarcomatoid carcinoma who were treated with platinum doublet chemotherapy.*

Patient number	Age	PS	Regimen	Treatment line	PFS (months)	OS (months)
1	39	1	CBDCA+nab-PTX	1	3.2	14.7
2	70	1	CBDCA+PTX+bevacizumab	1	4.1	16.2
3	73	2	CBDCA+nab-PTX	1	1.5	2.6
4	68	2	CBDCA+PTX	1	0.7	1.5
5	66	0	CBDCA+S-1	1	0.7	1.2

CBDCA: Carboplatin; nab-PTX: nanoparticle albumin-bound paclitaxel; PFS: progression-free survival; OS: overall survival; PS: performance status.

day at which disease progression or death was noted and was censored on the last day without any such events. OS was calculated from the day of treatment initiation until the day of death and censored at the last visit without death. The Kaplan–Meier curve was drawn, and the median survival time and 95% confidence interval (95%CI) were estimated. All statistical analyses were performed using JMP version 17.0.0 (SAS, Cary, NC, USA).

Results

A total of 60 patients with pulmonary sarcomatoid carcinoma were registered to our database. Of these, 40 patients were excluded because they were diagnosed based on surgical specimens or autopsy findings. Additionally, eight patients were excluded because they were not treated with either platinum-doublet chemotherapy or ICI therapy. Finally, 12 patients were included in the analysis. Eleven of the 12 patients were male, and all 12 patients had a smoking history. The median (range) age at which the systemic therapy was initiated was 67.5 (39–83) years. A driver mutation (MET exon14 skipping mutation) was detected using next-generation sequencing in one patient (Table I).

Of the 12 patients with pulmonary sarcomatoid carcinoma who were diagnosed using small specimens, five patients were treated with platinum-doublet chemotherapy. Table II shows the characteristics and survival of these five patients. PFS ranged from 0.7 to 4.1 months (median, 1.5 months; 95%CI=0.7-4.1 months). Four of the five patients were treated with ICIs in the later line of treatment. OS ranged from 1.2 to 16.2 months (median, 14.7 months; 95%CI=1.2-16.2 months). The Kaplan–Meier curves for PFS and OS after the initiation of the treatment with platinum-doublet chemotherapy are shown in Figure 1.

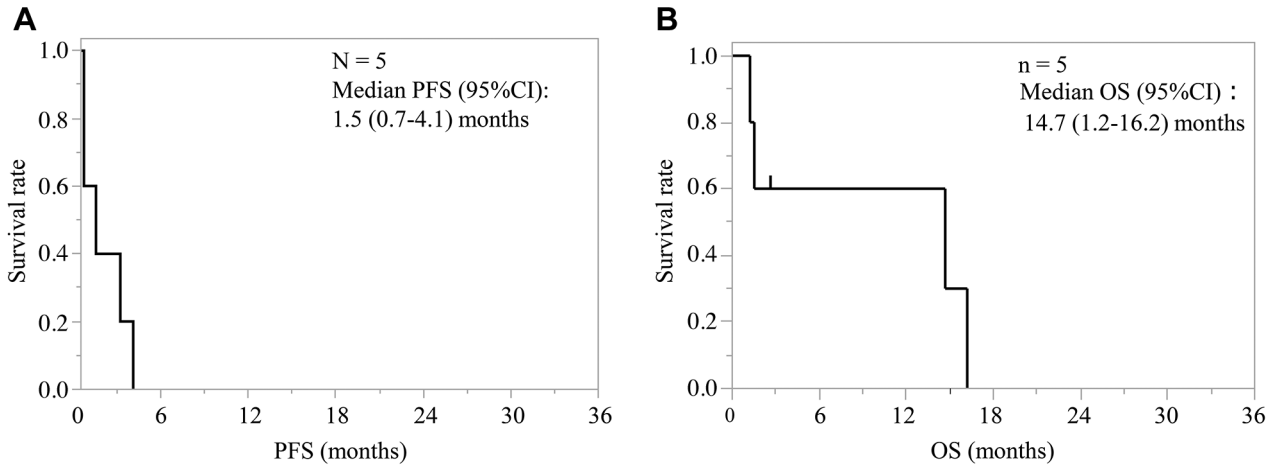

Figure 1. *Kaplan–Meier curves for survival duration after platinum-doublet chemotherapy. A) Progression-free survival, B) overall survival. Four of the five patients were subsequently treated with immune checkpoint inhibitor therapy.*

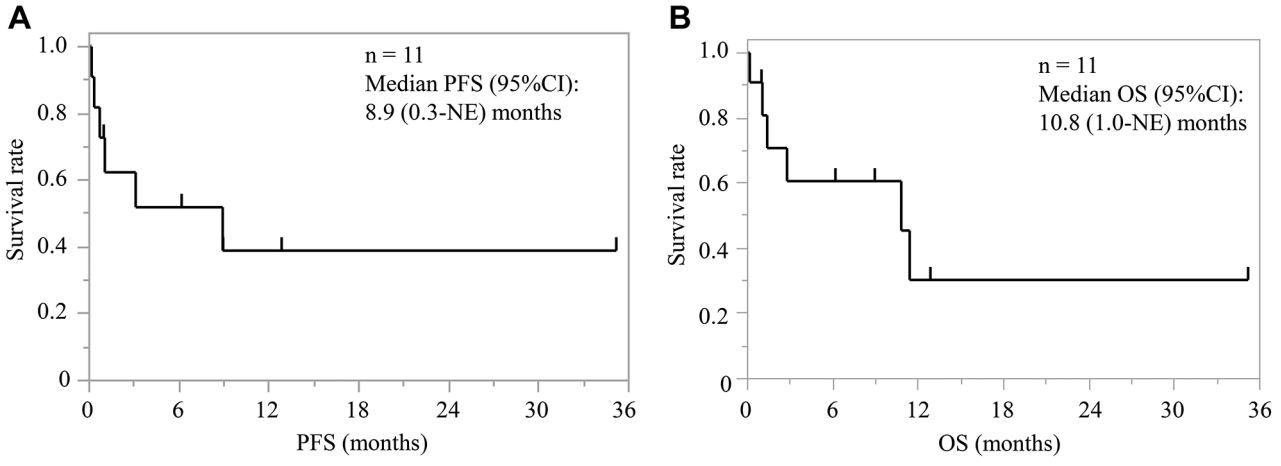

Figure 2. *Kaplan–Meier curves for survival duration after immune checkpoint inhibitor therapy. A) Progression-free survival, B) overall survival. NE: Not estimable.*

Of the 12 patients with pulmonary sarcomatoid carcinoma who were diagnosed using small specimens, 11 patients were treated with ICI therapy. Table III shows the characteristics and survival of these 11 patients. PFS after the initiation of the ICI therapy ranged from 0.3 to 35.2 (median, 8.9 months; 95%CI=0.3-not estimated). OS after the initiation of the ICI therapy ranged from 1.0 to 35.2 (median, 10.8 months; 95%CI=1.0-not estimated). Figure 2 shows the Kaplan–Meier curves for PFS and OS after the initiation of ICI therapy.

Discussion

Pulmonary sarcomatoid carcinoma is defined based on surgical specimens. However, advanced lung cancer is commonly diagnosed using small biopsies, which is often the case for patients with pulmonary sarcomatoid carcinoma (4, 5, 10, 11). The same issue applies to large-cell neuroendocrine carcinoma. Tokito *et al.* addressed this concern in patients with large-cell neuroendocrine carcinoma and reported the clinical

Table III. *Background and clinical course of patients with pulmonary sarcomatoid carcinoma who were treated with immune checkpoint inhibitor therapy.*

Patient number	Age	PS	Regimen	Treatment line	PFS (months)	OS (months)
1	40	1	Nivolumab	2	3.1	11.4
2	71	2	Nivolumab	3	0.7	2.8
3	73	3	Pembrolizumab	2	1.0*	1.0†
5	67	1	Pembrolizumab	2	0.2	0.2
6	82	1	Pembrolizumab	1	35.2*	35.2†
7	76	1	CBDCA+nab-PTX+atezolizumab	1	0.3	1.4
8	61	1	CBDCA+nab-PTX+atezolizumab	1	8.9	10.8
9	65	1	CBDCA+nab-PTX+pembrolizumab	1	6.2*	6.2†
10	83	3	Pembrolizumab	1	1.0	1.0
11	61	1	CBDCA+PTX+nivolumab+ipilimumab	1	8.9*	8.9†
12	67	2	Nivolumab+ipilimumab	1	12.8*	12.8†

CBDCA: Carboplatin; nab-PTX: nanoparticle albumin-bound paclitaxel; MET: mesenchymal-epithelial transition; PFS: progression-free survival; OS: overall survival; PS: performance status. *Without progression, †alive.

course of patients diagnosed using small biopsy specimens (12).

Twelve patients clinically diagnosed with pulmonary sarcomatoid carcinoma based on small biopsy specimens were enrolled in the present study. The patient characteristics, including age and smoking history, appeared to be similar to those reported in previous studies of pulmonary sarcomatoid carcinoma. Additionally, one of the 12 patients exhibited an MET exon14 skipping mutation, which is consistent with the known characteristics of the carcinoma (13, 14).

Pulmonary sarcomatoid carcinoma is generally recognized as chemoresistant. Previous studies focused on patients with pulmonary sarcomatoid carcinoma diagnosed using resection specimens have reported that the median cycles of cytotoxic chemotherapy were two or three (2, 3) and that the median PFS after the initiation of chemotherapy was 1.5 months (4). The present study demonstrated that the median PFS after chemotherapy in pulmonary sarcomatoid carcinoma clinically diagnosed using small biopsy specimens was 1.5 (95%CI=0.7-4.1) months, suggesting that they exhibit characteristics similar to those of previously reported pulmonary sarcomatoid carcinoma cases.

Moreover, several observational studies suggest that ICI therapy improves the prognosis of patients with pulmonary sarcomatoid carcinoma. Although the proportion of patients diagnosed using resection specimens varies, these studies have shown promising results (5-7). In the present study, although early progression or death occurred, the median PFS after ICI therapy was longer than that after chemotherapy. ICI therapy may also be recommended for patients with clinically diagnosed pulmonary sarcomatoid carcinoma using small biopsy specimens.

Based on these results, it is suggested that the characteristics of clinically diagnosed pulmonary sarcomatoid carcinoma using small biopsy specimens are similar to those diagnosed using resection specimens. However, the present study has several limitations. First, because the sample size was small, the results may not be representative of the general population, and random factors may have skewed the analysis. Second, given that the patients were clinically diagnosed using small biopsy specimens, there may have been other patients who showed sarcomatoid components in small specimens but were not diagnosed with sarcomatoid carcinoma. Therefore, it cannot be said that we evaluated the entire cohort of non-small cell carcinoma with spindle cell and/or giant cell carcinoma.

In summary, the present study suggests that the clinical course and characteristics of patients clinically

diagnosed with pulmonary sarcomatoid carcinoma using small biopsy specimens are consistent with those of patients diagnosed using resection specimens. Moreover, ICI therapy may improve the prognosis.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Minehiko Inomata performed data analysis and wrote the main text. Minehiko Inomata, Takeshi Tsuda, Nozomu Murayama, Zenta Seto, Kotaro Tokui, Seisuke Okazawa, and Ryuji Hayashi contributed to the interpretation of the data. Minehiko Inomata, Takeshi Tsuda, Tomomi Ichikawa, Masahiro Matsumoto, Isami Mizushima, Kenji Azechi, Naoki Takata, Nozomu Murayama, Zenta Seto, Kotaro Tokui, Yasuaki Masaki, Seisuke Okazawa, Shingo Imanishi, Toshiro Miwa, Ryuji Hayashi, and Hirokazu Taniguchi contributed to data collection.

Funding

No funding was received.

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