



# Effect of histological subtype on the efficacy of perioperative chemotherapy in pulmonary sarcomatoid carcinoma: a retrospective study based on SEER population

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**Background:** The efficacy of perioperative chemotherapy (PC) in pulmonary sarcomatoid carcinoma (PSC) is controversial. We conducted this study to investigate the effect of different histological subtypes on the efficacy of PC in PSC patients.

**Methods:** Clinicopathological data of 811 PSC patients of different histological subtypes were collected from the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan-Meier method and log-rank test were used to evaluate the effects of PC on the overall survival (OS) and cancer-specific survival (CSS) in different subtypes of PSC patients. Propensity score matching (PSM) was used to reduce potential confounding effects. Subgroup analyses were conducted to further investigate the efficacy of PC in patients with different characteristics.

**Results:** A total of 210 (25.89%) enrolled PSC patients received PC. PC was not associated with OS or CSS benefit in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma patients, neither before nor after matching. But survival benefit of PC was observed in carcinosarcoma patients both before (5-year OS: 48.79% *vs.* 38.75%,  $P=0.01$ ) and after (5-year OS: 51.29% *vs.* 17.54%,  $P=0.003$ ) matching. Subgroup analyses showed that in patients whose tumor larger than 4 cm, PC was still associated with improved survival in carcinosarcoma, but not in the other histological subtypes of PSC.

**Conclusions:** The efficacy of PC varies between different subtypes of PSC. Survival benefit of PC was only observed in carcinosarcoma patients, but not in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma patients. Histological subtype should be considered when treating PSC patients with PC.

**Keywords:** Pulmonary sarcomatoid carcinoma (PSC); carcinosarcoma; pleomorphic carcinoma; perioperative chemotherapy (PC)

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## Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of lung cancer characterized by aggressive malignancy. It accounts for less than 1% of lung cancer (1,2) and has worse prognosis than other types of lung cancer, with

a 5-year survival ranging from 12.3% to 25.1% based on different patient populations (3-6). According to the latest definition of World Health Organization (WHO), PSC consists of five histological subtypes—pleomorphic carcinoma, giant cell carcinoma, spindle cell carcinoma,

pulmonary blastoma, and carcinosarcoma—which are very different from other types of lung cancer in terms of morphology and content (7,8). The aggressiveness and heterogeneity have imposed challenges on the clinical treatment of PSC.

Surgery has been proved beneficial for survival and is now the standard treatment for non-advanced PSC patients (9,10). However, it was reported that the recurrence and metastasis rate was high even after complete resection (11,12). The addition of chemotherapy to surgery has been proposed to prevent recurrence and metastasis and to promote the prognosis, but the efficacy of additional chemotherapy is still controversial. Some studies reported the resistance for chemotherapy (11,13,14), while others favored chemotherapy for improved survival (15-17). But what is behind such different conclusions is largely unknown. Given that different histological subtypes of PSC might have distinct characteristics, we hypothesized that histological subtype might be a reason influencing the efficacy of additional chemotherapy. Herein, we conducted this study to investigate the effect of different subtypes of PSC on the efficacy of perioperative chemotherapy (PC) using the data from the Surveillance, Epidemiology, and End Results (SEER) database [2000–2020]. We present this article in accordance with the STROBE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-24-41/rc>).

### Highlight box

#### Key findings

- The histological subtype has an important effect on the efficacy of perioperative chemotherapy (PC) in pulmonary sarcomatoid carcinoma (PSC).

#### What is known and what is new?

- PSC consists of five histological subtypes. The efficacy of PC in PSC is controversial.
- We investigated the role of PC in 811 PSC patients of different histological subtypes, and found PC only brought survival benefit to carcinosarcoma patients (a PSC subtype), but not to patients of other subtypes.

#### What is the implication, and what should change now?

- Histological subtype is an important factor influencing the efficacy of PC in PSC, and this finding might explain the controversy about the role of PC in PSC patients. When making treatment strategy for PSC patients, especially when considering PC, physicians should take into account the histological subtype.

## Methods

### Data source

The SEER database is a U.S. population-based cancer database providing abundant clinicopathological information for most types of cancers. We retrospectively downloaded the data of interest using the software SEER Stat 8.4.2 (18). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### Patient enrollment

Eligible PSC patients diagnosed between 2000 to 2020 were enrolled. The site recode ICD-O-3/WHO 2008 was set as “Lung and Bronchus”; the ICD-O-3 code 8022 (pleomorphic carcinoma), 8031 (giant cell carcinoma), 8032 (spindle cell carcinoma), 8033 (pseudosarcomatous carcinoma), 8972 (pulmonary blastoma), and 8980 (carcinosarcoma) were used. Code 8033 (pseudosarcomatous carcinoma) meant that the tumor was diagnosed as PSC but the detailed histological subtype was not clear (19). The inclusion criteria of patients were: (I) aged  $\geq 18$  years; (II) histologically diagnosed with PSC; (III) underwent sublobectomy, lobectomy, or bilobectomy; (IV) tumor located in clear unilateral lobe; (V) clear survival time and cancer-specific survival (CSS) status. The exclusion criteria were: (I) unclear tumor size; (II) extended excision of the adjacent organ; (III) tumor of “distant” SEER summary stage; (IV) underwent pneumonectomy, which strongly indicated metastatic disease and severely impaired lung function; (V) the reporting source of “Autopsy only” or “Death certificate only”; (VI) underwent perioperative radiotherapy; (VII) incomplete clinical information.

### Variables and outcomes

We collected variables including age at which the patient was diagnosed with PSC, sex, race, year of diagnosis, primary tumor site, tumor size, surgery manner, differentiation grade, histological subtype, N stage, SEER summary stage (confirmed by the algorithm created by the SEER database: <https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/>), PC status, survival, survival status, and whether other in situ/malignant tumor developed before and after the diagnosis of PSC. The overall survival (OS) was defined as the duration of the diagnosis of PSC and the last follow-up or the death of any reasons. The CSS was

defined as the duration of the diagnosis of PSC and the last follow-up or the death because of the PSC.

### Survival analysis

To investigate the efficacy of PC and the effect of histological subtype on it, we not only compared the survival of all enrolled PSC patients with and without PC, but also conducted histological subtype-specific analyses. To reduce the potential confounding bias, we used propensity score matching (PSM) method to match the independent risk factors of survival between groups. Furthermore, subgroup analyses were conducted in the pleomorphic carcinoma, giant cell carcinoma, spindle cell carcinoma, and carcinosarcoma patients with certain clinicopathological characteristics.

### Statistical analysis

Continuous variables were converted into categorical variables using the cutoff values determined by X-tile tool. Categorical variables were described as absolute number and percentage and were analyzed using Pearson Chi-squared test. The Cox proportional hazards regression was used in the univariable and multivariable analyses to identify the independent risk factors of survival. Variables of  $P < 0.1$  in the univariable analysis were included into the multivariable analysis. Kaplan-Meier method was used in the survival analyses and the differences were tested by log-rank test. In the PSM, “MatchIt” R package was used and patients were matched at 1:1 ratio using “nearest” method. Hazard ratio (HR) and 95% confidence interval (CI) were used in the subgroup analyses to describe the effect of PC on the survival. The software used in this study was R (R-4.0.3).  $P < 0.05$  was considered significant and all  $P$  values were two tailed in our study.

## Results

### Patients and demographic characteristics

A total of 811 PSC patients were enrolled and 210 (25.89%) patients received PC. The median follow-up was 27 (interquartile range: 9–76.5) months. With respect to the treatment sequence of PC in those 210 patients, 166 (79.05%) were after surgery, 34 (16.19%) were unknown, and 10 (4.76%) were of other sequences. Compared to patients who only underwent surgery, patients who received PC were

younger (proportion of patients  $\geq 75$  years old: 35.3% *vs.* 16.2%,  $P < 0.001$ ), had larger tumors (proportion of tumors  $> 4$  cm: 37.3% *vs.* 61.9%,  $P < 0.001$ ), were less likely to undergo sublobectomy (proportion: 17.0% *vs.* 8.1%,  $P = 0.003$ ), had higher N stage (proportion of N1/N2: 13.0% *vs.* 31.9%,  $P < 0.001$ ), and were at a more advanced stage (proportion of summary stage “regional”: 46.9% *vs.* 64.3%,  $P < 0.001$ ). *Table 1* shows the demographic characteristics of patients. Among all enrolled PSC patients, 264 were pleomorphic carcinoma, 75 were giant cell carcinoma, 113 were spindle cell carcinoma, 21 were pulmonary blastoma, 115 were carcinosarcoma, and 223 were pseudosarcomatous carcinoma which meant detailed histological subtype was not clear other than PSC diagnosis. To better understand the effect of histological subtype on the efficacy of PC, the demographic characteristics of patients of different histological subtypes are shown in *Table 2*.

### Survival analysis before PSM

Of patients who only underwent surgery, the 1-, 3-, 5-year OS rate were 70.96%, 51.95%, 44.22% respectively, and the 1-, 3-, 5-year CSS rate were 76.68%, 61.64%, 55.15% respectively. Of patients who received PC, the 1-, 3-, 5-year OS rate were 83.45%, 62.15%, 49.71% respectively, and the 1-, 3-, 5-year CSS rate were 85.36%, 65.58%, 58.43% respectively. In all enrolled patients, PC was associated with better OS (*Figure 1A*,  $P = 0.02$ ), but not when it came to CSS (*Figure 1B*,  $P = 0.24$ ). In specific histological subtype, PC showed no benefit for OS or CSS in pleomorphic carcinoma patients (*Figure 1C, 1D*), giant cell carcinoma patients (*Figure 1E, 1F*), or spindle cell carcinoma patients (*Figure 1G, 1H*). However, in carcinosarcoma patients, PS was associated with improved OS (*Figure 1I*,  $P = 0.01$ ) and CSS (*Figure 1J*,  $P = 0.04$ ). In pulmonary blastoma patients, although the result seemed that PC might bring survival benefit to them, the difference was not statistically significant due to the small sample size (*Figure S1*). In pseudosarcomatous carcinoma patients who were diagnosed with PSC but without detailed histological subtype, PC was associated with better OS (*Figure 1K*,  $P = 0.02$ ), but not as to CSS (*Figure 1L*,  $P = 0.11$ ).

### Survival analysis after PSM

The result of univariable and multivariable analyses showed that age, sex, year of diagnosis, tumor size, histological subtype, N stage, summary stage, and chemotherapy were

**Table 1** The demographic characteristics of enrolled PSC patients

Characteristics	Surgery (N=601)	Surgery + chemotherapy (N=210)	P
Age (years)			<0.001
<65	168 (28.0)	87 (41.4)	
65–74	221 (36.8)	89 (42.4)	
≥75	212 (35.3)	34 (16.2)	
Sex			0.72
Female	270 (44.9)	98 (46.7)	
Male	331 (55.1)	112 (53.3)	
Race			0.52
White	521 (86.7)	180 (85.7)	
Black	50 (8.3)	22 (10.5)	
Others <sup>†</sup>	30 (5.0)	8 (3.8)	
Year of diagnosis			<0.001
2000–2006	174 (29.0)	32 (15.2)	
2007–2013	224 (37.3)	76 (36.2)	
2014–2020	203 (33.8)	102 (48.6)	
Primary site			0.44
Right upper lobe	199 (33.1)	71 (33.8)	
Right middle lobe	34 (5.7)	12 (5.7)	
Right lower lobe	110 (18.3)	39 (18.6)	
Left upper lobe	165 (27.5)	46 (21.9)	
Left lower lobe	93 (15.5)	42 (20.0)	
Size (cm)			<0.001
≤2	129 (21.5)	18 (8.6)	
2–4	248 (41.3)	62 (29.5)	
4–6	119 (19.8)	62 (29.5)	
>6	105 (17.5)	68 (32.4)	
Surgery			0.003
Sublobectomy	102 (17.0)	17 (8.1)	
Lobectomy/bilobectomy	499 (83.0)	193 (91.9)	
Differentiation			0.34
Well/moderately differentiated	26 (4.3)	5 (2.4)	
Poorly differentiated	320 (53.2)	115 (54.8)	
Undifferentiated	88 (14.6)	38 (18.1)	
Unknown	167 (27.8)	52 (24.8)	

**Table 1** (continued)**Table 1** (continued)

Characteristics	Surgery (N=601)	Surgery + chemotherapy (N=210)	P
Histological subtype			0.17
Pseudosarcomatous carcinoma	164 (27.3)	59 (28.1)	
Pleomorphic carcinoma	189 (31.4)	75 (35.7)	
Giant cell carcinoma	57 (9.5)	18 (8.6)	
Spindle cell carcinoma	93 (15.5)	20 (9.5)	
Pulmonary blastoma	18 (3.0)	3 (1.4)	
Carcinosarcoma	80 (13.3)	35 (16.7)	
N stage			<0.001
N0	482 (80.2)	128 (61.0)	
N1	49 (8.2)	40 (19.0)	
N2	29 (4.8)	27 (12.9)	
NX <sup>‡</sup>	41 (6.8)	15 (7.1)	
Summary stage <sup>§</sup>			<0.001
Localized	319 (53.1)	75 (35.7)	
Regional	282 (46.9)	135 (64.3)	
Other malignancy <sup>¶</sup>			0.29
No	322 (53.6)	122 (58.1)	
Yes	279 (46.4)	88 (41.9)	

Values are numbers (percentages), and percentages may not total 100 because of rounding. “2–4 cm” of tumor size indicates that the tumor size was between 2 cm (not included) and 4 cm (included). So does the expression “4–6 cm”. <sup>†</sup>, others included Asian/Pacific Islander and American Indian/Alaska Native; <sup>‡</sup>, NX indicated that the N stage could not be assessed or the N stage was unknown; <sup>§</sup>, stage confirmed by the algorithm created by the SEER database. For more information: <https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/>; <sup>¶</sup>, whether developed other in situ/malignant tumor before and after the diagnosis of PSC. PSC, pulmonary sarcomatoid carcinoma; SEER, Surveillance, Epidemiology, and End Results.

independent risk factors of OS or CSS (Tables S1,S2). And the risk factors were matched between the surgery only and the surgery plus chemotherapy groups in the survival comparison. The clinicopathological characteristics of the matched groups were balanced (Table 3, Tables S3–S7, Figures S2–S7).

In patients of all subtypes of PSC, PC was associated with better OS (Figure 2A, P<0.001) and CSS (Figure 2B, P=0.005). In specific histological subtype, PC still showed

**Table 2** The demographic characteristics of different subtypes of PSC patients

Characteristics	Pleomorphic carcinoma (N=264)	Giant cell carcinoma (N=75)	Spindle cell carcinoma (N=113)	Pulmonary blastoma (N=21)	Carcinosarcoma (N=115)
Age (years)					
<65	73 (27.7)	38 (50.7)	39 (34.5)	14 (66.7)	34 (29.6)
65–74	112 (42.4)	20 (26.7)	44 (38.9)	2 (9.5)	45 (39.1)
≥75	79 (29.9)	17 (22.7)	30 (26.5)	5 (23.8)	36 (31.3)
Sex					
Female	114 (43.2)	28 (37.3)	56 (49.6)	16 (76.2)	58 (50.4)
Male	150 (56.8)	47 (62.7)	57 (50.4)	5 (23.8)	57 (49.6)
Race					
White	225 (85.2)	61 (81.3)	100 (88.5)	17 (81.0)	98 (85.2)
Black	28 (10.6)	8 (10.7)	8 (7.1)	3 (14.3)	12 (10.4)
Others <sup>†</sup>	11 (4.2)	6 (8.0)	5 (4.4)	1 (4.8)	5 (4.3)
Year of diagnosis					
2000–2006	32 (12.1)	35 (46.7)	54 (47.8)	12 (57.1)	41 (35.7)
2007–2013	88 (33.3)	25 (33.3)	24 (21.2)	6 (28.6)	36 (31.3)
2014–2020	144 (54.5)	15 (20.0)	35 (31.0)	3 (14.3)	38 (33.0)
Primary site					
Right upper lobe	95 (36.0)	31 (41.3)	32 (28.3)	3 (14.3)	37 (32.2)
Right middle lobe	13 (4.9)	5 (6.7)	11 (9.7)	0 (0.0)	7 (6.1)
Right lower lobe	39 (14.8)	10 (13.3)	27 (23.9)	9 (42.9)	23 (20.0)
Left upper lobe	67 (25.4)	21 (28.0)	25 (22.1)	3 (14.3)	30 (26.1)
Left lower lobe	50 (18.9)	8 (10.7)	18 (15.9)	6 (28.6)	18 (15.7)
Size (cm)					
≤2	48 (18.2)	13 (17.3)	27 (23.9)	1 (4.8)	19 (16.5)
2–4	110 (41.7)	28 (37.3)	46 (40.7)	7 (33.3)	38 (33.0)
4–6	63 (23.9)	19 (25.3)	22 (19.5)	3 (14.3)	24 (20.9)
>6	43 (16.3)	15 (20.0)	18 (15.9)	10 (47.6)	34 (29.6)
Surgery					
Sublobectomy	45 (17.0)	8 (10.7)	17 (15.0)	5 (23.8)	13 (11.3)
Lobectomy/bilobectomy	219 (83.0)	67 (89.3)	96 (85.0)	16 (76.2)	102 (88.7)
Differentiation					
Well/moderately differentiated	2 (0.8)	1 (1.3)	7 (6.2)	9 (42.9)	3 (2.6)
Poorly differentiated	165 (62.5)	30 (40.0)	53 (46.9)	2 (9.5)	53 (46.1)
Undifferentiated	39 (14.8)	24 (32.0)	13 (11.5)	1 (4.8)	15 (13.0)
Unknown	58 (22.0)	20 (26.7)	40 (35.4)	9 (42.9)	44 (38.3)

Table 2 (continued)

Table 2 (continued)

Characteristics	Pleomorphic carcinoma (N=264)	Giant cell carcinoma (N=75)	Spindle cell carcinoma (N=113)	Pulmonary blastoma (N=21)	Carcinosarcoma (N=115)
N stage					
N0	195 (73.9)	60 (80.0)	97 (85.8)	5 (23.8)	66 (57.4)
N1	44 (16.7)	7 (9.3)	8 (7.1)	0 (0.0)	8 (7.0)
N2	25 (9.5)	5 (6.7)	7 (6.2)	0 (0.0)	7 (6.1)
NX <sup>‡</sup>	0 (0.0)	3 (4.0)	1 (0.9)	16 (76.2)	34 (29.6)
Summary stage <sup>§</sup>					
Localized	104 (39.4)	38 (50.7)	71 (62.8)	15 (71.4)	55 (47.8)
Regional	160 (60.6)	37 (49.3)	42 (37.2)	6 (28.6)	60 (52.2)
Chemotherapy					
No/unknown	189 (71.6)	57 (76.0)	93 (82.3)	18 (85.7)	80 (69.6)
Yes	75 (28.4)	18 (24.0)	20 (17.7)	3 (14.3)	35 (30.4)
Other malignancy <sup>¶</sup>					
No	152 (57.6)	46 (61.3)	54 (47.8)	12 (57.1)	69 (60.0)
Yes	112 (42.4)	29 (38.7)	59 (52.2)	9 (42.9)	46 (40.0)

Values are numbers (percentages), and percentages may not total 100 because of rounding. “2–4 cm” of tumor size indicates that the tumor size was between 2 cm (not included) and 4 cm (included). So does the expression “4–6 cm”. †, others included Asian/Pacific Islander and American Indian/Alaska Native; ‡, NX indicated that the N stage could not be assessed or the N stage was unknown; §, stage confirmed by the algorithm created by the SEER database. For more information: <https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/>; ¶, whether developed other in situ/malignant tumor before and after the diagnosis of PSC. PSC, pulmonary sarcomatoid carcinoma; SEER, Surveillance, Epidemiology, and End Results.

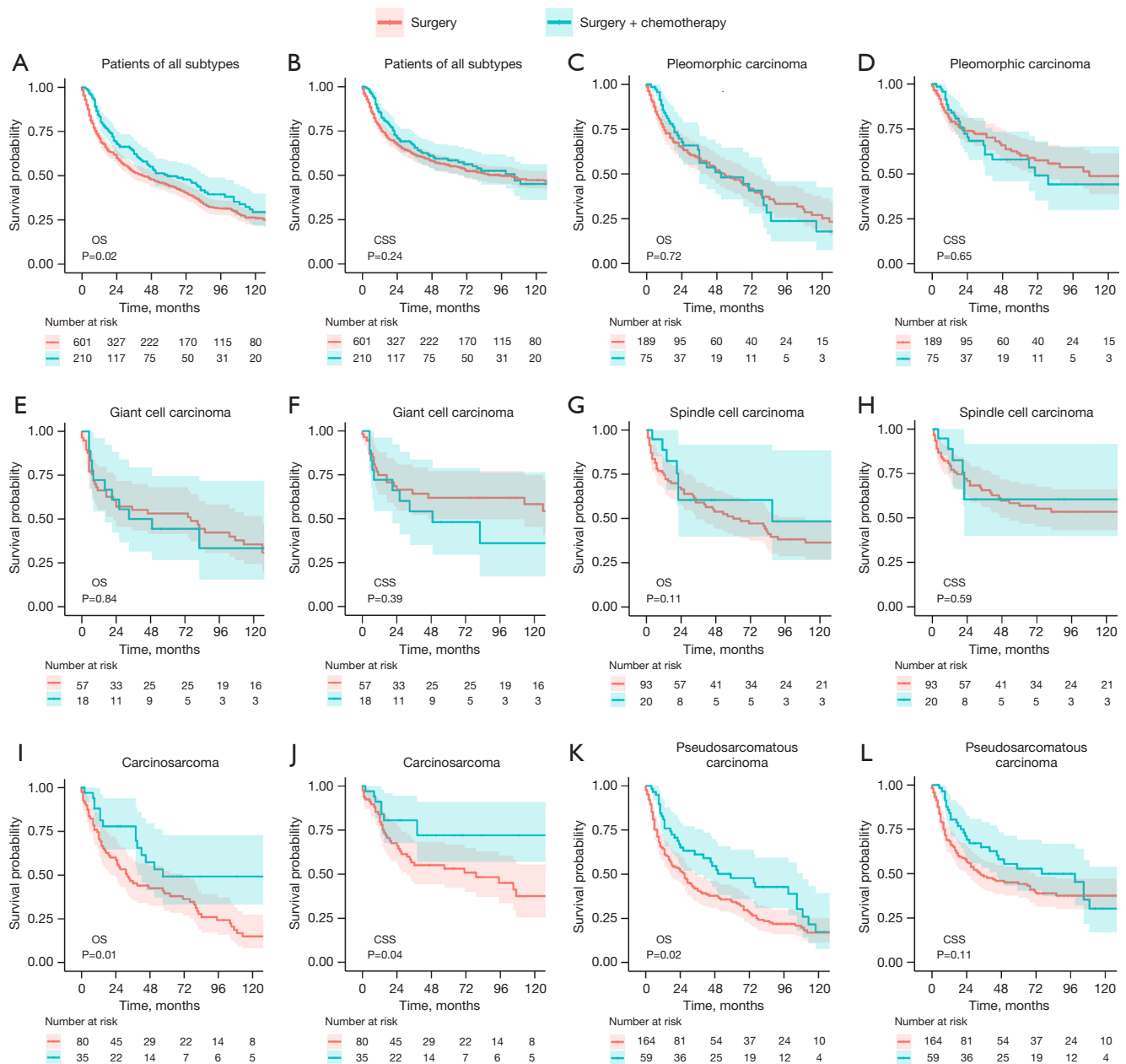
no benefit for OS or CSS in pleomorphic carcinoma patients (Figure 2C,2D), giant cell carcinoma patients (Figure 2E,2F), or spindle cell carcinoma patients (Figure 2G,2H). Meanwhile, in carcinosarcoma patients, PS was still associated with improved OS (Figure 2I, P=0.003) and CSS (Figure 2J, P=0.008). In pseudosarcomatous carcinoma patients, PC showed no significant benefit for OS (Figure 2K, P=0.06) nor CSS (Figure 2L, P=0.07). As for pulmonary blastoma patients, we did not conduct survival analysis after matching because of the small sample size.

### Subgroup survival analyses

To further validate our findings, we conducted histological subtype-specific subgroup analyses according to age, sex, tumor size, surgery manner, summary stage, and other malignancy status (Figure 3; Figure S8). In carcinosarcoma patients, apart from the ≤4 cm subgroup and the sublobectomy subgroup, PC appeared to be associated with

improved OS across all subgroups, although the differences were not significant in some subgroups, possibly due to the small sample size in each subgroup. In pleomorphic carcinoma patients and giant cell carcinoma patients, no significant association between PC and survival was found across subgroups. In spindle cell carcinoma patients, there seemed to be a trend suggesting potential survival benefit from the PC, but the effect was not significant, which might also be due to the small sample size.

Because PC was more often recommended for tumors >4 cm, we further conducted survival comparison in patients with tumors >4 cm. Consistently, the survival of carcinosarcoma patients who received PC was better as compared to patients who did not (before PSM: P<0.001, Figure 3E; after PSM: P=0.001, Figure 3I). In pleomorphic carcinoma patients and giant cell carcinoma patients, no significant benefit from PC was found neither before nor after match (Figure 3B,3C,3E,3G). In spindle cell carcinoma patients, PC was associated with better OS before PSM



**Figure 1** Survival comparison of patients who received perioperative chemotherapy or not in different subtypes of PSC before matching. (A,B) All subtypes of PSC; (C,D) pleomorphic carcinoma; (E,F) giant cell carcinoma; (G,H) spindle cell carcinoma; (I,J) carcinosarcoma; (K,L) pseudosarcomatous carcinoma. PSC, pulmonary sarcomatoid carcinoma; OS, overall survival; CSS, cancer-specific survival.

(Figure 3D,  $P=0.03$ ) but not after PSM (Figure 3H,  $P=0.12$ ).

### Discussion

PSC is characterized by its aggressive malignancy and poor prognosis and whether PC could improve the survival of

PSC patients has been a controversial topic. We investigated the effect of different histological subtypes of PSC on the efficacy of PC and found that survival benefit of PC was only observed in carcinosarcoma patients but not in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma neither before nor after PSM. For pulmonary blastoma

**Table 3** The characteristics of carcinosarcoma patients after matching

Characteristics	Surgery (N=35)	Surgery + chemotherapy (N=35)	P
Age (years)			0.76
<65	12 (34.3)	15 (42.9)	
65–74	17 (48.6)	15 (42.9)	
≥75	6 (17.1)	5 (14.3)	
Sex			> 0.99
Female	18 (51.4)	19 (54.3)	
Male	17 (48.6)	16 (45.7)	
Race			0.48
White	32 (91.4)	29 (82.9)	
Black	3 (8.6)	6 (17.1)	
Year of diagnosis			0.36
2000–2006	11 (31.4)	6 (17.1)	
2007–2013	9 (25.7)	12 (34.3)	
2014–2020	15 (42.9)	17 (48.6)	
Primary site			0.85
Right upper lobe	12 (34.3)	13 (37.1)	
Right middle lobe	4 (11.4)	2 (5.7)	
Right lower lobe	8 (22.9)	6 (17.1)	
Left upper lobe	7 (20.0)	9 (25.7)	
Left lower lobe	4 (11.4)	5 (14.3)	
Size (cm)			0.51
≤2	3 (8.6)	2 (5.7)	
2–4	14 (40.0)	10 (28.6)	
4–6	8 (22.9)	7 (20.0)	
>6	10 (28.6)	16 (45.7)	
Surgery			>0.99
Sublobectomy	4 (11.4)	3 (8.6)	
Lobectomy/bilobectomy	31 (88.6)	32 (91.4)	
Differentiation			0.69
Well/moderately differentiated	1 (2.9)	1 (2.9)	
Poorly differentiated	14 (40.0)	19 (54.3)	
Undifferentiated	5 (14.3)	4 (11.4)	
Unknown	15 (42.9)	11 (31.4)	

**Table 3** (continued)**Table 3** (continued)

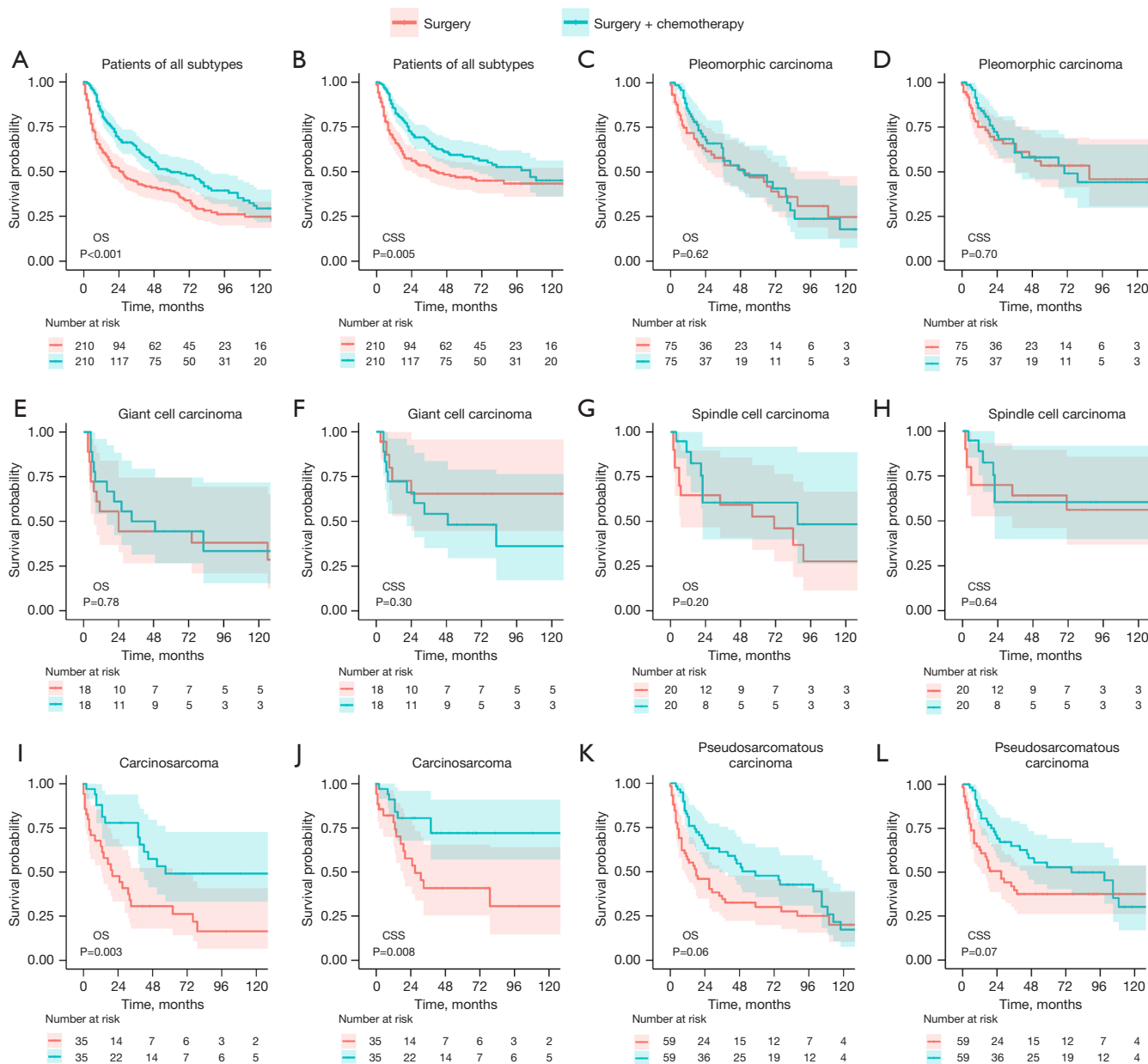
Characteristics	Surgery (N=35)	Surgery + chemotherapy (N=35)	P
N stage			0.96
N0	18 (51.4)	18 (51.4)	
N1	3 (8.6)	4 (11.4)	
N2	4 (11.4)	3 (8.6)	
NX <sup>‡</sup>	10 (28.6)	10 (28.6)	
Summary stage <sup>§</sup>			0.81
Localized	16 (45.7)	14 (40.0)	
Regional	19 (54.3)	21 (60.0)	
Other malignancy <sup>¶</sup>			0.62
No	24 (68.6)	21 (60.0)	
Yes	11 (31.4)	14 (40.0)	

Values are numbers (percentages), and percentages may not total 100 because of rounding. “2–4 cm” of tumor size indicates that the tumor size was between 2 cm (not included) and 4 cm (included). So does the expression “4–6 cm”. <sup>‡</sup>, NX indicated that the N stage could not be assessed or the N stage was unknown; <sup>§</sup>, stage confirmed by the algorithm created by the SEER database. For more information: <https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/>; <sup>¶</sup>, whether developed other in situ/malignant tumor before and after the diagnosis of PSC. PSC, pulmonary sarcomatoid carcinoma; SEER, Surveillance, Epidemiology, and End Results.

patients, PC appeared to be beneficial but the difference was not significant because of the small sample size.

Due to the rarity of PSC, no prospective randomized controlled trial has investigated the potential of PC to improve the prognosis of PSC patients. In the recent decades, several retrospective studies have explored this problem but reported opposite results. On one hand, some studies found that PSC patients could not benefit from PC (9,11,13,14,20). In the study by Karim *et al.*, the median OS of patients who received PC was even shorter than that of patients who received surgery only (457.6 *vs.* 713.5 days), though the difference was not significant (14). In the study by Huang *et al.*, PC was associated with better survival in the univariable analysis but not in the multivariable analysis (21). On the other hand, some studies reported that PC could improve the survival of PSC patients (2,3,15–17,22). Among these studies, some found that the survival benefit of PC was observed in stage II/III patients, but not in stage I patients (2,3,15,16). This difference might



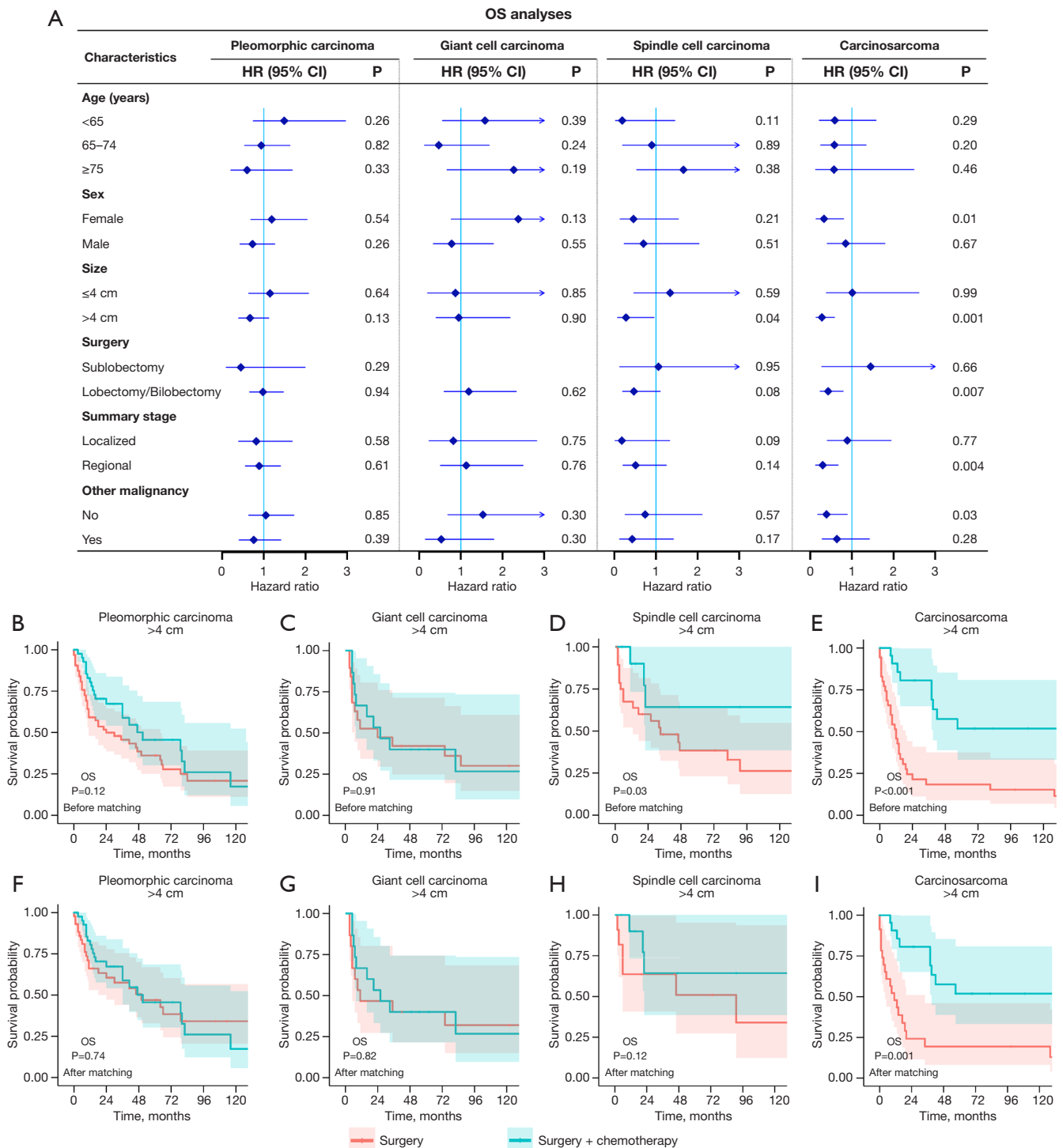


**Figure 2** Survival comparison of patients who received perioperative chemotherapy or not in different subtypes of PSC after matching. (A,B) All subtypes of PSC; (C,D) pleomorphic carcinoma; (E,F) giant cell carcinoma; (G,H) spindle cell carcinoma; (I,J) carcinosarcoma; (K,L) pseudosarcomatous carcinoma. PSC, pulmonary sarcomatoid carcinoma; OS, overall survival; CSS, cancer-specific survival.

be a result of the influence of confounding factors, as some studies included patients with metastasis, some included patient who received radiotherapy, some included patients who underwent pneumonectomy, and some utilized PSM method or multivariable analysis while others did not.

In terms of histological subtype, in studies that did not support the use of PC, only two studies described the

proportion of each subtype of PSC and the proportion of carcinosarcoma in their enrolled patients was less than 1% (9,11). In studies favoring PC, *Cen et al.* reported a 12.4% proportion of carcinosarcoma in their study. However, in the subgroup analysis they found that PC was not associated survival benefit in all five WHO-defined specific subtypes of PSC, including carcinosarcoma (16).



**Figure 3** Subgroup overall survival analysis in different subtypes of PSC. (A) Forest plots; (B,F) pleomorphic carcinoma patients whose tumor >4 cm, before and after matching; (C,G) giant cell carcinoma patients whose tumor >4 cm, before and after matching; (D,H) spindle cell carcinoma patients whose tumor >4 cm, before and after matching; (E,I) carcinosarcoma patients whose tumor >4 cm, before and after matching. PSC, pulmonary sarcomatoid carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Their finding in carcinosarcoma patients was different from ours. In their study, they enrolled patients of stage IV and patients who underwent pneumonectomy, meanwhile, whether the characteristics of carcinosarcoma patients in the subgroup analysis of the PC group and the surgery only group were balanced was not reported. In our study, patients with advanced stage and patients who received pneumonectomy or extended lobectomy were excluded, and the characteristics of carcinosarcoma patients between groups were balanced after PSM. These heterogeneity between the two studies might account for the difference.

According to the definition of WHO, pleomorphic carcinoma is a poorly differentiated non-small cell lung cancer (NSCLC, including squamous cell carcinoma, adenocarcinoma), or undifferentiated NSCLC that contains at least 10% spindle and/or giant cells or a carcinoma consisting only of spindle and giant cells (8). Spindle cell carcinoma and giant cell carcinoma are almost entirely composed of epithelial spindle cells and malignant giant cells, respectively, without differentiated carcinomatous elements (8). In our study, although in the three subtypes, PC was not associated with better survival, it seemed that spindle cell carcinoma patients were more likely to benefit from PC as compared to giant cell carcinoma patients, especially spindle cell carcinoma patients whose tumor size >4 cm. In the study by Hendriksen *et al.*, they reported that PC was beneficial in stage II/III/IV but not in stage I pleomorphic carcinoma patients (3). In our subgroup analysis about tumor stage, PC was neither associated with better survival in stage “localized” pleomorphic carcinoma patients nor in stage “regional” pleomorphic carcinoma patients. Due to the significant variation in the proportion of spindle cells, giant cells, and other tumor cells in pleomorphic carcinoma, the internal heterogeneity between pleomorphic carcinomas was evident (23). This heterogeneity might result in the difference between our study and their study. And we agree that further studies taking into account of the cellular composition of pleomorphic carcinoma are needed.

The diagnosis of PSC was mainly based on morphology and immunohistochemistry as needed. Pleomorphic carcinoma, spindle cell carcinoma, and giant cell carcinoma did not contain true sarcomatous element and rarely express markers of sarcomatous differentiation in the immunohistochemistry, while pulmonary blastoma and carcinosarcoma did (8,24). In the study by Weissferdt *et al.*, they proposed that the conflicting results of

clinicopathologic features and prognostic data might result from the heterogeneous composition of PSC, and in their study, carcinosarcoma and pulmonary blastoma were considered as different clinicopathologic entities from the other three subtypes (23). Our result supported this opinion and emphasized the importance of histological subtype when considering PC.

In addition to the difference in morphology and immunohistochemistry, different molecular profiles of each subtype of PSC have been identified. Studies found that pleomorphic carcinoma was prone to have *KRAS* mutation or *EGFR* mutation, while these mutations rarely present in carcinosarcoma (25-30). And it has been reported that *KRAS* mutation was associated with resistance to chemotherapy (31). Nowadays, in the era of target therapy and immunotherapy, studies have tried to uncover the characteristic of targetable driven mutations and immune checkpoints (32-34). *MET* exon alteration has been found to be more enriched in PSC than in other NSCLC and has been suggested as a promising targetable mutation (32). But the *MET* mutation in carcinosarcoma also seems to be rare (25). Studies take into account the molecular profiles and histological subtypes of PSC to investigate the efficacy of PC might help individualize treatment in the future.

There were some limitations in our study. First, our study was a retrospective study and selection bias might exist. Second, although in the subgroup analysis spindle cell carcinoma patients whose tumor >4 cm were likely to benefit from PC, we could not investigate the reason behind it as no more pathological information or molecular profile information was available. Third, due to the lack of information in the SEER database, we could not assess whether the type of drug (platinum-based *vs.* non-platinum-based), dosage, and duration of PC might affect our findings. Fourth, it was widely reported that the smoking rate was high in PSC patients (4,9,10), but we could not evaluate the effect of smoking on the efficacy of PC because there was also no smoking information in the SEER database.

With regard to statistics, there were also some limitations to note in our study. First, because PSC is a rare disease, the sample size of each histological subgroup is limited, though our study was already based on a database of large sample size. No benefit of PC was found in pleomorphic carcinoma patients, giant cell carcinoma patients, or spindle cell carcinoma patients in our study, but it should be noted that there might be a lack of statistical power due to the

small sample size. Second, in the subgroup analysis, the sample size further decreased, so the result of subgroup analyses might only be suitable for investigating the trend of effect rather than evaluating the absolute effect. Third, as we conducted numerous survival comparisons among PSC patients of different histological subtypes, there might be a multiplicity issue in our study, which suggested that the small P value observed in carcinosarcoma patients was merely a chance finding. But as discussed above, pleomorphic carcinoma, spindle cell carcinoma, and giant cell carcinoma did not contain true sarcomatous element but carcinosarcoma did. Based on the histological characteristic, the possibility that our finding was just a chance finding resulting from multiplicity issue was slim.

## Conclusions

We investigated the effect of different histological subtypes of PSC on the efficacy of PC and found that significant survival benefit of PC was only observed in carcinosarcoma patients. Our findings shed light on the important role of histological subtype when considering PC for PSC patients. Further studies evaluating the efficacy of PC based on the molecular profiles might help with individualized treatment in the future.

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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