Pathologic Findings and Long-Term Results After Surgical Treatment for Pulmonary Sarcomatoid Tumors: A Multicenter Analysis

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Background. **Pulmonary sarcomatoid carcinoma (PSC) is a very rare subtype of non-small cell lung cancer (NSCLC). The aim of this study was to clarify the pathologic characteristics and long-term survival after surgical treatment in patients with PSC.**

Methods. **From January 2003 to December 2013, we retrospectively reviewed the clinical findings, surgical notes, and pathologic and follow-up data from 148 consecutive patients who underwent curative resection for PSC in 5 institutions. The Kaplan-Meier method, log-rank test, and Cox regression analysis were used.**

Results. **Mean age and male to female ratio were 66.6 ± 9.9 years and 120:28, respectively. Surgical resection (pneumonectomy in 8 patients, bilobectomy in 132 patients, and sublobar resection in 8 patients) was complete in 142 cases (96%). At pathologic evaluation, 36 patients (24%) had stage I, 69 patients (47%) had stage II, 33 patients (22%) had stage III, and 10 patients (7%) had stage IV disease. A "biphasic tumor" (PSC with an NSCLC component) was observed in 77 patients (52%). We detected a high rate of vascular emboli in the surgical specimens (overall, 68%; 57% in pathologic stage I tumors), whereas lymphatic emboli were found in 30% of cases (5% of pathologic stage I tumors). Overall median and 5-year long-term survival (LTS) was 19 months and 12.6% (LTS, 16.3% in pathologic stage I), respectively. Distant recurrences frequently occurred after surgical treatment (81%), even in pathologic stage I tumors that underwent R0 resection (62%). Multivariable survival analysis identified R+ resection (hazard ratio [HR],12.3; 95% confidence interval [CI], 3.67–41.28; $p < 0.0001$), advanced pathologic stage (HR, 5.75; 95% CI, 2.55–12.98; $p < 0.0001$), and the presence of vascular emboli (HR, 1.67; 95% CI, 1.05–2.67; $p = 0.0327$) as independent negative prognostic factors.**

Conclusions. **PSCs have very aggressive behavior and high metastatic potential even in early stages. R+ resection, pathologic TNM status, and the presence of vascular emboli are independent prognostic factors.**

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Pulmonary sarcomatoid carcinoma (PSC) is a subset of non-small cell lung cancer (NSCLC) characterized by the presence of a sarcoma-like or heterologous sarcoma component. It composes approximately 0.4% of all pulmonary malignancies according to analysis of the Surveillance, Epidemiology, and End Results database [1]. Because of its inherent rarity, systematic reports concerning this type of lung cancer are uncommon and, accordingly, the clinical decision-making process has been based on clinicopathologic descriptions of small case series or single case reports [2, 3]. Current treatment options for PSC, especially for advanced cases, are limited to surgical treatment, despite poor long-term results after surgical resection [3, 4]. Nonsurgical modalities also represent a challenge for oncology practitioners, because the sensitivity of these tumors to the current medical approaches, including platinum-based doublets, sarcoma-specific regimens, or radiotherapy, is disappointing [5]. Finally, the lack of PSC-oriented clinical trials has severely hindered the recognition of tailored and more effective treatments beyond operation [5, 6].

The biological behavior and clinical course of sarcomatoid carcinomas of the lung are poorly documented,

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and some authors have reported dismal outcomes for PSC in single-institution studies (11%–21% 5-year survival rate), worse than those observed for stage-matched conventional NSCLC [3, 7]. We established a multi-institutional collaboration among 5 tertiary thoracic surgery centers to evaluate the histopathologic characteristics, treatment modalities, and long-term survival of patients with PSC. The outcome of this analysis is reported here.

Patients and Methods

Among 6,569 consecutive patients who underwent curative resection for NSCLC from January 2003 to December 2013 at 5 institutions (IRCCS-Arcispedale Santa Maria Nuova of Reggio Emilia, IRCCS-Regina Elena of Rome, University Hospital Policlinico of Modena, Catholic University of Rome, and Forlanini Hospital of Rome), 148 (2.2%) had PSC and formed the basis of this retrospective analysis.

Because diagnosis of sarcomatoid carcinoma through precise histopathologic examination requires surgical resection, patients with a diagnosis of PSC based on cytologic examination (nonsurgical cases) or those undergoing surgical intervention for diagnostic purposes only were excluded from this analysis.

Before undertaking our data analysis, we obtained institutional review board approval from the promoting center (IRCCS-Arcispedale Santa Maria Nuova of Reggio Emilia) for the research use of retrospectively collected data (observational) stemming from standard clinical practice.

Data related to sex, age, signs and symptoms, laboratory test results, tumor location and stage, surgeons' notes, pathologic features, postoperative therapy, recurrence patterns, and long-term follow-up were systematically reviewed and recorded (Tables 1, 2).

Preoperative Evaluation

In all of the patients, the preoperative evaluation included medical history reporting, physical examination, routine blood tests, standard chest roentgenologic and thoracic computed tomography (CT). Fluorodeoxyglucose-18 positron emission tomography/CT (^{18}F-FDG PET/CT) was not routinely performed during the study period (Table 1).

Surgical Treatment

Despite some unavoidable variability in the surgical technique among the 5 centers involved, the surgical policy adopted when planning the pulmonary resection extension was based on similar assumptions, which follow:

1. Parenchymal resection to a lesser extent than a lobectomy was considered oncologically inappropriate and was never performed in "clinically fit" patients.
2. Sublobar resection (segmentectomy or wedge resection) was indicated only in patients judged "clinically unfit" for lobar resection.
3. Lymph node dissection (lobe specific or complete) was performed in all cases, and the mediastinal tissue encompassing the lymph nodes was dissected and removed systematically within typical anatomic landmarks.

Table 1. Clinical and Surgical Findings of the Population

Features	Total Sample = 148
Age (mean ± SD)	66.6 ± 9.9 y
Sex	
Male/female	120/28 (81%/19%)
Side of tumor	
Right/left	83/65 (56%/44%)
^{18F}FDG-PET/CT scan	
Yes	76 (51%)
No	72 (49%)
SUV_{max} (mean ± SD)	15.2 ± 5.5
Preoperative diagnosis	
Yes	56 (38%)
No	92 (62%)
Tumor size (mean ± SD)	5.8 ± 3.1 cm
Induction therapy	4 (3%)
Surgical procedure	
Sublobar resection	8 (5%)
Lobectomy/bilobectomy	132 (90%)
Pneumonectomy	8 (5%)
Postoperative mortality/complications	3/41 (2%/28%)
Completeness of resection	
R0	142 (96%)
R+	6 (4%)

^{18F}FDG-PET/CT = fluorine-18 positron emission tomography/computed tomography; R0 = complete resection; R+ = R1 and R2; SUV_{max} = maximum standardized uptake value.

The resection was considered complete (R0) according to the criteria proposed by the International Association for the Study of Lung Cancer Staging Committee [8].

Pathologic Features

The surgical pathologic stage was assigned using the seventh edition of the TNM classification system according to the International Staging System for Lung Cancer [9], and data from patients observed and treated before its introduction into clinical practice have been updated to cohere with this classification system and to obtain homogeneous staging information throughout the entire cohort.

A centralized blind pathologic revision of the samples was performed by an expert pathologist specializing in lung pathology (G.R.) to avoid any variations in the pathologic diagnosis and to achieve substantial concordance with the histopathologic characteristics of the samples evaluated. The revision was performed according to the revised 2015 World Health Organization classification of lung tumors [10], on which the following diagnostic criteria are based. In detail, "biphasic PSC" (Fig 1) appears as a biphasic neoplasm with a well-differentiated carcinoma component intermingled with a sarcomatoid component (at least 10% of the tumor). Otherwise, the tumor presents without obvious epithelial differentiation on routine microscopy, consisting only of a

Table 2. Pathologic Features, Postoperative Treatment, and Pattern of Relapse

Pathologic staging	
I	36 (24%)
II	69 (47%)
III	33 (22%)
IV	10 (7%)
Lymph node involvement	
N0	98 (66%)
N1	26 (18%)
N2	24 (16%)
LN (N1 + N2) removed (mean ± SD)	9.2 ± 5.8
LN (N1 + N2) neoplastic (mean ± SD)	1.1 ± 3.4
Histologic subtype	
Pleomorphic	92 (62%)
Spindle cell	42 (29%)
Giant cell	12 (8%)
Carcinosarcoma	2 (1%)
Blastoma	0 (0%)
Pathologic features	
Biphasic tumors (combined with NSCLC)	77 (52%)
Lymphatic invasion	45 (30%)
Vascular invasion	100 (68%)
Postoperative treatment	
Chemotherapy[a]	99 (67%)
Radiotherapy[a]	43 (29%)
None	44 (30%)
Relapse of disease	104 (70%)
Local[b]	60 of 104 (58%)
Distant[b]	84 of 104 (81%)

[a] 38 patients underwent combined chemotherapy/radiotherapy. [b] 40 patients had both local and distant relapse of disease.

LN = lymph node; NSCLC = non-small cell lung cancer.

pure sarcomatoid component ("pure PSC") (Fig 1). Moreover, during specimen revision, we identified and distinguished 5 different variants of PSC (pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma). Examples of sarcomatoid carcinoma on pathologic evaluation are also seen in Figure 1. Briefly, pleomorphic carcinoma is defined as NSCLC combined with neoplastic spindle or giant cells (or both) or a carcinoma consisting only of spindle and giant cells. Spindle cell carcinoma is a carcinoma composed exclusively of spindle-shaped tumor cells, whereas giant cell carcinoma is composed of neoplastic highly pleomorphic giant cells. In carcinosarcoma, a carcinoma component is combined only with a sarcoma, the latter consisting of heterologous elements, such as malignant cartilage, bone, or muscle. Finally, pulmonary blastoma is a biphasic tumor in which both the epithelial and mesenchymal components have a primitive "fetal-type" appearance.

The presence of vascular emboli (V-EM) or lymphatic emboli (L-EM) was assessed by standard hematoxylin and eosin staining of samples from tumor and adjacent nontumoral lung tissue and was defined as the presence of tumor cell aggregates inside vascular (Fig 2) or lymphatic microvessels. Blood vessels were distinguished from lymphatic vessels by the presence of either erythrocytes in the lumen or elastic fibers in the vascular wall.

Postoperative Treatment and Follow-Up

Patients received adjuvant platinum-based chemotherapy or radiotherapy (or both) under the care of referring oncologists. The clinical records from outpatient clinics and correspondence with the patient's referring physician provided information about the health status of the patient. Follow-up data were available for all patients.

Aims

The main aim of this study was to better define the clinicopathologic characteristics and long-term results in patients with PSC after curative resection. In addition, we aimed to identify significant prognostic factors influencing long-term outcomes.

Statistical Analysis

Descriptive statistical analysis was performed to investigate the sample characteristics. Means ± standard deviation were used to summarize continuous variables, whereas absolute and relative frequencies (n, %) were used for categorical variables (Tables 1 and 2). Differences in the means of continuous variables between groups were assessed by the Student's *t* test, whereas the χ^2 test was used to analyze the distribution of categorical variables. Overall survival was investigated by the Kaplan-Meier method. The log-rank test was applied to compare survival curves according to demographic, lifestyle, and clinical factors. Simple Cox regression analysis was also performed to estimate the hazards ratio (HR) of the following potential prognostic factors: age, sex, and the predominant clinical, surgical, and pathologic features (Table 2). Multivariable survival analysis using a Cox regression model was performed to evaluate the following variables: age, sex, surgical radicality, presence of vascular emboli, histologic features, and pathologic stage. The selected variables were evaluated for possible interactions in a correlation matrix, and all the interactions with a correlation coefficient greater than or equal to 0.5 were incorporated into the model. The threshold for statistical significance was set at p less than 0.05. SPSS, version 13 for Windows (SPSS Inc, Chicago, IL) and Stata, version 12.1 for Windows (StataCorp LP, College Station, TX) were used for the statistical analyses.

Results

Demographics and clinical and pathologic features are summarized in Tables 1 and 2. A preoperative diagnosis was achieved in approximately half of the cases (56 patients [38%]) through CT-guided (25 patients) or fiberoptic bronchoscopic biopsy (31 patients). In 25 cases, frozen-section pathologic examination was performed, and among these cases, only 5 (20%) had a presumptive diagnosis of sarcomatoid carcinoma.

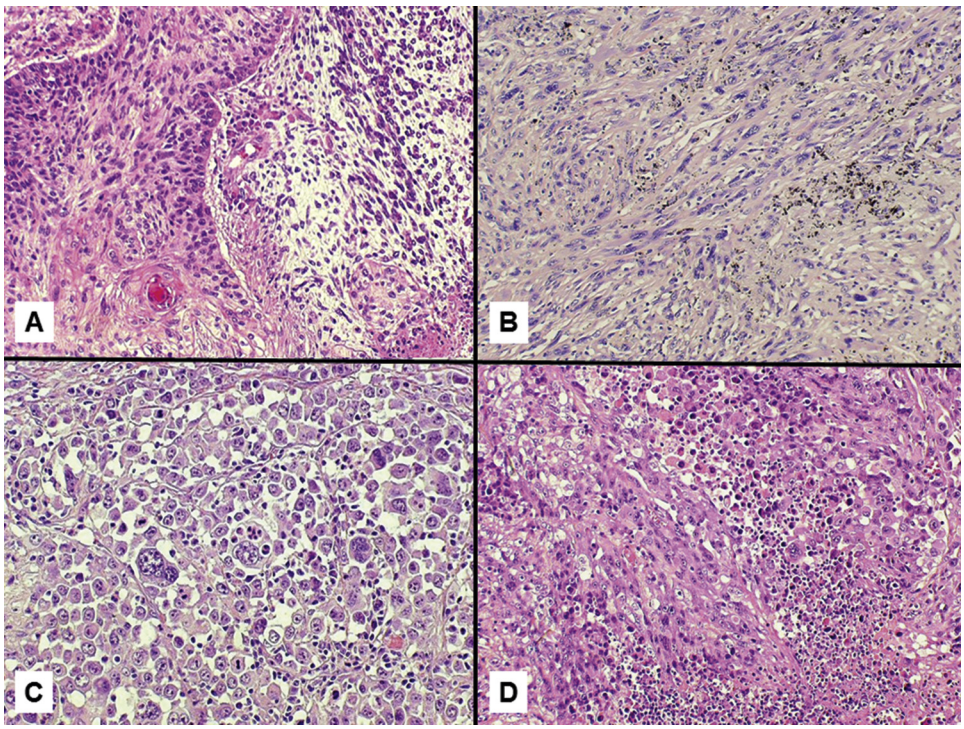

Fig 1. Examples of sarcomatoid carcinoma. (A) Pleomorphic carcinoma (hematoxylin-eosin; ×150 magnification) composed of conventional (NSCLC) (eg, squamous cell carcinoma, on left) and spindle cell carcinoma (on right). (B) Pure spindle cell carcinoma (hematoxylin-eosin; ×200 magnification). (C) Pure giant cell carcinoma (hematoxylin-eosin; ×200 magnification). (D) Mixed spindle cell and giant cell carcinoma (hematoxylin-eosin; ×200 magnification).

The mean maximum standardized uptake value (SUV_{max}) was 15.2 ± 5.5 (range, 6–29), with 15 patients (30%) presenting with a very high SUV_{max} value (>17). Only 4 patients (2.7%) underwent induction platinum-based chemotherapy for pathologically proven N2 disease, and they underwent operative treatment after radiologic restaging (approximately 4 weeks after the end of induction platinum-based chemotherapy). Lobectomy was the main surgical procedure performed, and complete resection was obtained in a high percentage of cases (96%). Extended resection to adjacent organs (chest wall in 10 cases, pericardium in 2 cases, and

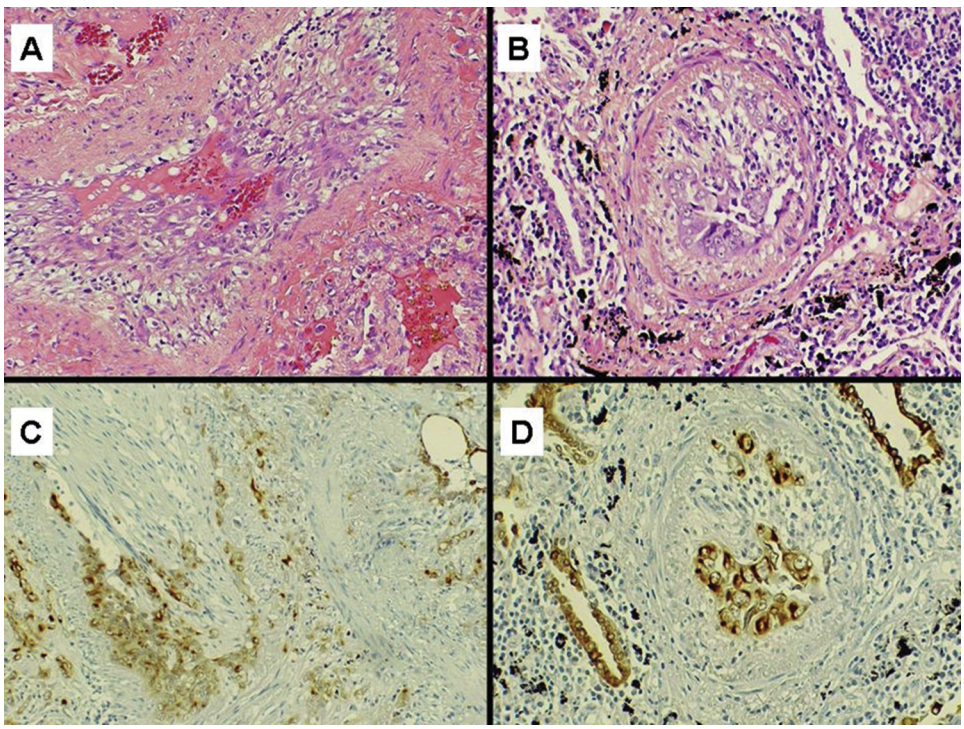

Fig 2. (A and B) Vascular invasion by sarcomatoid carcinoma occluding the vessels (hematoxylin-eosin; ×200 magnification). (C and D) Pan cytokeratin (clone AE1/AE3) stain (immunohistochemistry; ×200 magnification).

diaphragm in 1 case) was performed in 13 (9%) patients, whereas sublobar resection was performed in patients with poor pulmonary function (8 patients).

The χ^2 test revealed a statistically significant correlation between the dimension of the tumor and achievement of R0 resection and found that tumor size greater than 5 cm was associated with a tumor not being radically removed ($p = 0.0293$). Similarly, we observed that "extended resection" (lung resection combined with resection of 1 of more neighboring organs, ie, the chest wall) was associated more frequently with R+ resection ($p = 0.0008$).

Pathologic involvement of mediastinal lymph nodes was found in approximately 16% of patients, whereas a biphasic tumor was observed in 77 patients (52%). In detail, the NSCLC component consisted of adenocarcinoma in 42 patients, squamous cell carcinoma in 24 patients, adenosquamous carcinoma in 6 patients, and large cell carcinoma in 5 patients. There were no significant differences in SUV_{max} between tumors with and those without an NSCLC component (mean SUV_{max}, 15.23 in pure PSC versus mean SUV_{max}, 15.21 in biphasic PSC; $p = 0.834$).

We observed a high rate of V-EM (68%) in the surgical specimens, whereas L-EM was found in about 30% of samples. Moreover, even when considering early-stage cases (pT1/2N0M0, 54 patients), V-EM was present in a significantly high proportion of cases (57.4%), whereas L-EM was detected in only 5.4%.

After surgical treatment, 3 deaths occurred postoperatively (1 resulting from acute septicemia, 1 caused by massive pulmonary embolism, and 1 from cardiac failure after pneumonectomy). Atrial fibrillation (19 cases), pneumonia (11 cases), and prolonged air leaks (9 cases) were the main postoperative complications. The postoperative treatments are summarized in Table 2.

Patterns of Recurrence and Long-Term Survival

During the follow-up (mean, 67 months; range, 6–103 months), 104 patients (70%) experienced disease recurrence. Among them, distant relapse occurred more frequently than local relapse (81% versus 58%), considering that 40 patients had both local and distant relapse. Among patients with pathologic stage I who underwent R0 resection (n = 36), 22 patients (61%) presented with distant metastases during follow-up.

Overall survival data are presented in Figure 3. Considering the entire cohort of patients, the median survival time and 5-year LTS rate were 19 months and 12.6% (95% confidence interval [CI], 5.2%–17.4%], respectively. The log-rank test (Table 3; Fig 4) identified the clinical TNM stage, surgical completeness, pathologic TNM status, and disease relapse as factors significantly associated with survival. A nonsignificant trend ($p = 0.092$) was seen when comparing the survival of patients with the pure versus biphasic types of PSC and, similarly, ($p = 0.137$) when comparing the LTS of patients with PSC with V-EM versus those without V-EM (Fig 4D).

The radiometabolic pattern (SUV_{max} <15 versus SUV_{max} >15) did not influence the prognosis regarding long-term survival. Finally, adjuvant chemotherapy did not provide any significant survival advantage, even after the entire cohort was stratified by stage of disease.

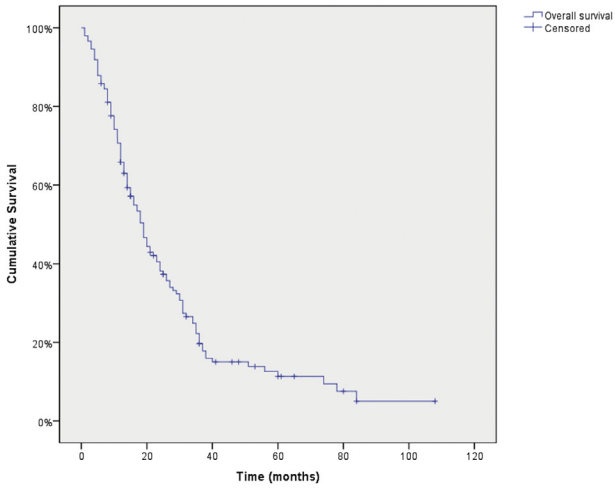

Fig 3. Overall long-term survival (LTS) in entire cohort of patients.

Age, sex, and other covariates that were significant or borderline ($p < 0.20$) in the Kaplan-Meier univariable analysis of survival were evaluated in a multivariable survival analysis using a Cox regression model (Table 3). In multivariable analysis, surgical incompleteness (HR, 12.3; 95% CI, 3.67–41.28; $p < 0.0001$), advanced pathologic stage (HR, 5.75; 95% CI, 2.55–12.98; $p < 0.0001$), and the presence of vascular emboli (HR, 1.67; 95% CI, 1.05–2.67; $p = 0.0327$) were associated with worse survival.

Comment

The results of this multicenter study of a large population of surgically treated patients with PSC may be summarized as follows. First, a high rate of V-EM was detected, even in early-stage tumors, and this factor significantly impacted the prognosis in such patients. Second, the LTS results were not satisfactory (LTS rate, 12.6%) after surgical treatment, even in patients with pathologic stage I (LTS rate, 16.3%). Moreover, distant relapse also occurred frequently in patients with pathologic stage I who underwent R0 resection. Finally, surgical completeness (R0 resection) and pathologic staging significantly affected the long-term outcomes of patients with PSC.

Clinical Presentation and Diagnosis

In the current series, 2.2% of all NSCLC cases treated by curative resection consisted of PSC, which is in line with other research (2.35% [11]). Moreover, as reported previously [4], we observed a higher prevalence of male patients (male to female ratio, 5:1), and the overall mean age of the patients was 67 years.

Radiologically, PSCs usually do not present with unusual radiologic features besides the common detection of radiologic signs of necrosis [3] and a certain predilection to grow in a peripheral location and invade the chest wall [7, 11]. In our experience and in line with that of others [7, 11], chest wall resection was required in 10 cases (~7% of cases).

Table 3. Survival Results: Univariable and Multivariable Analysis

	Univariable Analysis (Log-Rank Test)		Multivariable Analysis (Cox Hazard Model of Factors Affecting Survival)	
Features	5-y LTS (95% CI)	*p* Value	HR (95% CI)	*p* Value
Sex				
Male	11.7% (4.8–18.6)	0.990	0.80 (0.45–1.44)	0.462
Female	9.8% (0–22.5)			
Age, y				
<65	8% (0.3–15.6)	0.243	0.98 (0.97–1.01)	0.131
>65	14.2% (4.7–23.6)			
PET SUV_{max} (n = 76)			. . .	. . .
<15	25.7% (3.7–47.6)	0.282		
>15	32.9% (12.7–53.1)			
Clinical stage			. . .	. . .
I	20.3% (6.1–34.4)	**<0.0001**		
II	11.3% (2.9–19.7)			
III	0%			
IV	0%			
Surgical radicality				
R0	11.8% (5.5–18.1)	**<0.0001**	12.3 (3.67–41.28)	**<0.0001**
R+	0%			
Tumor size			. . .	. . .
<5 cm	9% (1.4–16.6)	0.476		
≥5 cm	14.9% (5.5–24.3)			
Histologic features				
Pure tumors	5.3% (0–11.4)	0.092	0.89 (0.58–1.36)	0.592
Biphasic tumors	18% (7.6–28.4)			
Histologic subtypes			. . .	. . .
Pleomorphic	15.1% (6.5–23.7)	0.216		
Spindle cell	2.6% (0–7.5)			
Giant cell	35.7% (5.9–65.5)			
Carcinosarcoma	0% (–)			
Vascular emboli				
Yes	10.9% (2.5–19.3)	0.137	1.67 (1.05–2.67)	**0.0327**
No	22.4% (8.8–35.9)			
Lymphatic emboli			. . .	. . .
Yes	11.3% (1.1–21.5)	0.514		
No	15.2% (5.4–25)			
Pathologic T status			. . .	. . .
pT1	30.6% (0–62.7)	**<0.0001**		
pT2	10.1% (10.8–19.1)			
pT3	8.5% (0.4–16.5)			
pT4				
Pathologic N status			. . .	. . .
pN0	13.4% (5.2–21.6)	0.539		
pN1	0%			
pN2	14.9% (0–30.2)			
Pathologic M status				
pM0	12% (5.5–18.5)	**<0.0001**		
pM1	0%			
Pathologic stage				
pI	10.8% (0–23.5)	**<0.0001**	5.75 (2.55–12.98)	**<0.0001**
pII	12.5% (3.1–21.9)			
pIII	11.5% (0–23.4)			
pIV	0%			

(*Continued*)

Table 3. Continued

Features	Univariable Analysis (Log-Rank Test) 5-y LTS (95% CI)	*p* Value	Multivariable Analysis (Cox Hazard Model of Factors Affecting Survival) HR (95% CI)	*p* Value
Adjuvant chemotherapy			. . .	. . .
Yes	6.6% (0.9–12.3)	0.293		
No	23.2% (9.5–36.7)			
Adjuvant radiotherapy			. . .	. . .
Yes	11.4 (0–24.5)	0.820		
No	11.8% (4.9–18.6)			
Relapse of disease			. . .	. . .
Yes	2.5 (0–5.8)	**<0.0001**		
No	34.2 (17.5–50.8)			

Boldface values are statistically significant.

CI = confidence interval; HR = hazard ratio; LTS = long-term survival; PET = positron emission tomography; R0 = complete resection; R+ = R1 and R2; SUV_{max} = maximum standardized uptake value.

A reliable diagnosis of PSC depends substantially on morphologic characteristics and immunohistochemical staining. As noted by other authors [4], the preoperative diagnosis and, even more so, the intraoperative frozen pathologic findings are often inconsistent with the definitive pathologic diagnosis. In the present study, we obtained a certain diagnosis before the surgical procedure in less than half of the cases (38%); however, this rate was even higher than those reported previously (11.6% [4], 29.4% [12], and 22.7% [11]). Finally, PSC presented a very high level of ^{18F}FDG uptake (mean SUV_{max}, 15) on ^{18F}FDG-PET/CT, but no specific radiometabolic patterns were found in relation to histologic subtype.

Long-Term Survival, Pathologic Characteristics, and Pattern of Recurrence

The 5-year survival rate (LTS) reported for patients with PSC varies between 11% and 24.5% [3, 4, 12, 13], and it was 12.6% in our cohort. This rate appears to be substantially worse than that commonly observed in NSCLC cases, as already noted by several other authors [1, 3, 7]; good LTS stratification according to surgical completeness and pathologic stage of disease was achieved (both $p < 0.0001$).

Although a high metabolic uptake could indicate high biological aggressiveness of such a rare disease, the SUV_{max} value does not seem capable of discriminating among different prognostic subsets of patients.

A difference in LTS was also observed in the comparison of pure PSC and biphasic PSC (LTS rates, 5% versus 18%, respectively), although such a difference did not reach statistical significance ($p = 0.092$) and was not confirmed by the multivariable analysis (Table 3). In line with this, Pelosi and colleagues [14] previously showed that the aggressive nature of sarcomatoid carcinoma is, at least in part, attributed to the sarcomatoid elements, which may enhance angiogenic activity as well as tumor cell motility.

Interestingly, we found a very high rate of V-EM (68%) in the surgical specimens, higher than the L-EM rate (30%). This difference in V-EM and L-EM was further increased in the evaluation of the early-stage cases only (57% versus 5%). Similar results were obtained by Yuki and colleagues [15], who reported frequent vascular invasion (57.1%) in patients with PSC with pN0 disease. Survival multivariable analysis showed that the presence of V-EM in PSC specimens was independently correlated with a worse LTS (Table 3). However, and in contrast to NSCLC, the N stage of disease did not significantly impact LTS (13.4% in patients with pN0 disease versus 14.9% in patients with pN2 disease).

Concerning the pattern of relapse, a certain body of evidence suggests that distant metastasis occurs more frequently than does local relapse in these neoplasms [3, 7, 13]. Our analysis confirmed this, with a very high rate of distant relapse observed, even in early-stage tumors (61%).

Therefore, considering the unusual pathologic and oncologic characteristics of PSCs (high rate of V-EM, frequent occurrence of distant relapse, and no prognostic impact of the N factor), we speculate that hematogenous spread may be preferred to lymphatic spread in such rare tumors. This biological behavior differs substantially from conventional NSCLCs and is more similar to high-grade sarcomas or sarcoma-like neoplasms.

Adjuvant Therapy

In patients with NSCLC, platinum-based combination regimens are the standard of care as adjuvant chemotherapy for high-risk patients with stage IB, II, and IIIA, together with palliative chemotherapy [16–18].

Otherwise, no standard effective treatment for PSC is available because of the rarity of this disease, and scarce literature is available regarding its molecular status. Previous reports have indicated that advanced PSC responds poorly to chemotherapy [19, 20]. In our cohort, 99 patients received adjuvant chemotherapy and did not show a long-term survival advantage compared with patients who did not. However, several confounding selection biases should be considered with regard to this finding.

Because of the poor prognosis of PSC and considering that platinum-based chemotherapy has traditionally

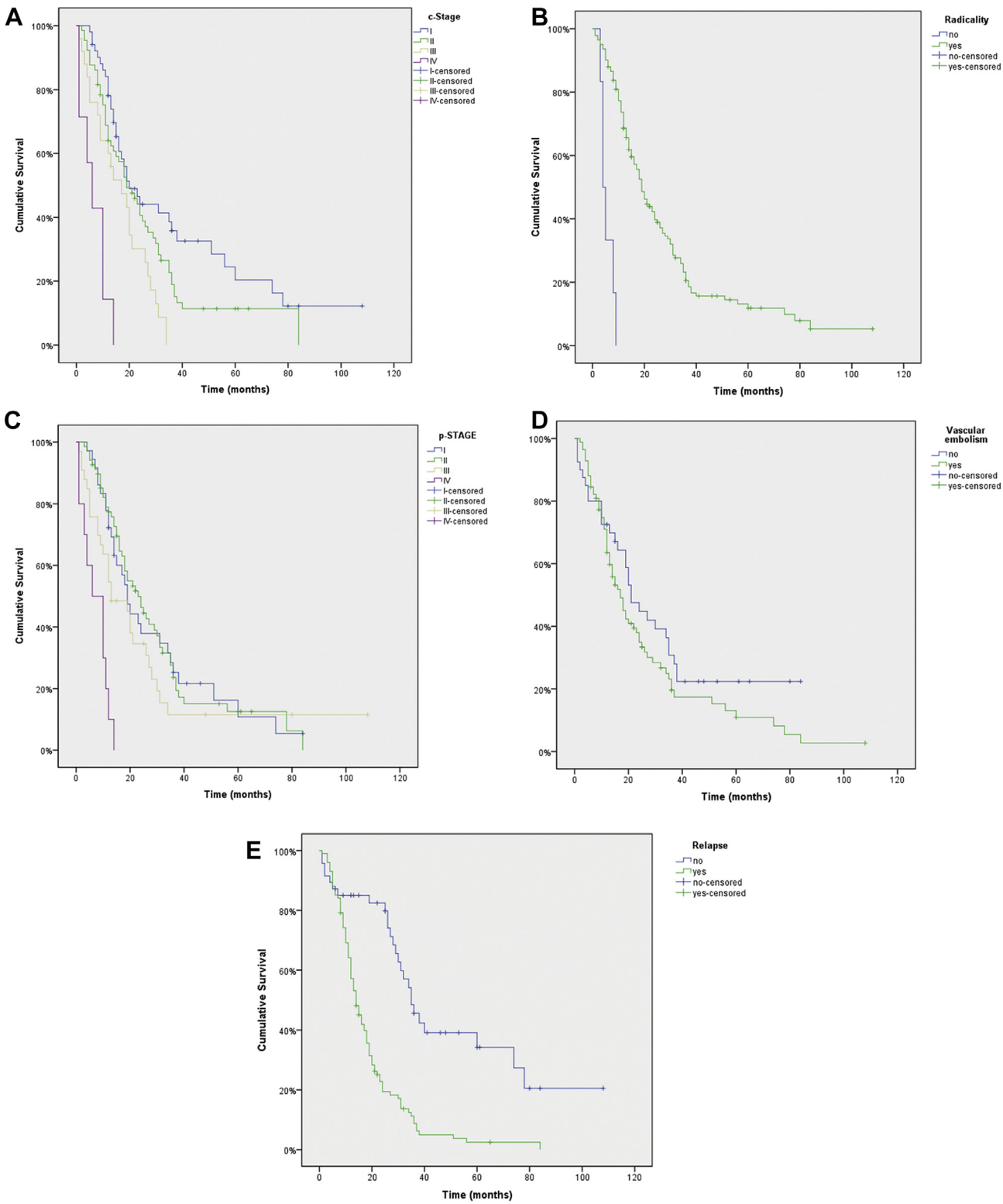

Fig 4. Long-term survival (LTS) function according to (A) clinical stage (c-stage), (B) surgical radicality), (C) pathologic stage (p-stage), (D) presence of vascular emboli, and (E) occurrence of tumor relapse.

shown low efficacy, identification of an effective chemotherapy regimen is important, and the best regimen for PSC still needs to be determined.

Limitations, Points of Strength, and Future Perspectives

The retrospective nature of the analysis limits the strength of the results, and this should be considered by

readers when conferring clinical value to the reported evidence. Moreover, data collection from different centers represents an additional significant limitation. However, the collection of a relatively large clinical series of an uncommon entity and the consistent review by a single expert pathologist are 2 crucial aspects that add weight to our conclusions.

Considering the poor response to standard drugs and the questionable role of surgical treatment, the current optimal treatment for such an entity has yet to be defined. In this setting, the investigation of the molecular profile of PSC (not yet well defined [21–25]) is urgently needed. A recent study by Fallet and colleagues [25] demonstrated the presence of multiple mutations in approximately 40% of PSCs, including "druggable" genes such as *EGFR* (22%). In this sense, we have planned an ongoing project consisting of DNA mutation sequencing of PSC samples using next-generation systems for better molecular profiling of such rare tumors.

Conclusions

PSCs are rare neoplasms with very aggressive behavior and high metastatic potential, as suggested by the high presence of vascular embolisms in the surgical specimens and frequent occurrence of distant relapses, even after radical resection of early-stage tumors. The surgical completeness, pathologic TNM status, and presence of vascular emboli were independent prognostic factors in our cohort.

Considering the remarkable biological aggressiveness of these neoplasms, physicians should use caution in recommending surgical resection (especially in the case of pneumonectomy) for patients with PSC. As we await new more effective systemic therapies, adjuvant therapies may be indicated that are different from those used for NSCLC, even for early-stage tumors, along with strict radiologic surveillance.

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References

1. Yendamuri S, Caty L, Pine M, et al. Outcomes of sarcomatoid carcinoma of the lung: a Surveillance, Epidemiology, and End Results Database analysis. Surgery 2012;152:397–402.
2. Sato Y, Saito N, Endo S, et al. Resection of a pleomorphic carcinoma of the lung invading the descending aorta. J Thorac Cardiovasc Surg 2004;127:1829–30.
3. Venissac N, Pop D, Lassalle S, Berthier F, Hofman P, Mouroux J. Sarcomatoid lung cancer (spindle/giant cells): an aggressive disease? J Thorac Cardiovasc Surg 2007;134:619–23.
4. Lin Y, Yang H, Cai Q, et al. Characteristics and prognostic analysis of 69 patients with pulmonary sarcomatoid carcinoma. Am J Clin Oncol 2016;39:215–22.
5. Pelosi G, Gasparini P, Cavazza A, et al. Multiparametric molecular characterization of pulmonary sarcomatoid carcinoma reveals a nonrandom amplification of anaplastic lymphoma kinase (ALK) gene. Lung Cancer 2012;77:507–14.
6. Ichihara S, Toyooka S, Fujiwara Y, et al. The impact of epidermal growth factor receptor gene status on gefitinib-treated Japanese patients with non-small-cell lung cancer. Int J Cancer;120:1239–47.
7. Martin LW, Correa AM, Ordonez NG, et al. Sarcomatoid carcinoma of the lung: a predictor of poor prognosis. Ann Thorac Surg 2007;84:973–80.
8. Rami-Porta R, Wittekind C, Goldstraw P, International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25–33.
9. Goldstraw P, Crowley JJ, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:706–14.
10. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2015:78–9.
11. Park JS, Lee Y, Han J, et al. Clinicopathologic outcomes of curative resection for sarcomatoid carcinoma of the lung. Oncology 2011;81:206–13.
12. Huang SY, Shen SJ, Li XY. Pulmonary sarcomatoid carcinoma: a clinicopathologic study and prognostic analysis of 51 cases. World J Surg Oncol 2013;11:252.
13. Raveglia F, Mezzetti M, Panigalli T, et al. Personal experience in surgical management of pulmonary pleomorphic carcinoma. Ann Thorac Surg 2004;78:1742–7.
14. Pelosi G, Fraggetta F, Nappi O, et al. Pleomorphic carcinomas of the lung show a selective distribution of gene products involved in cell differentiation, cell cycle control, tumor growth, and tumor cell motility: a clinicopathologic and immunohistochemical study of 31 cases. Am J Surg Pathol 2003;27:1203–15.
15. Yuki T, Sakuma T, Ohbayashi C, et al. Pleomorphic carcinoma of the lung: a surgical outcome. J Thorac Cardiovasc Surg 2007;134:399–404.
16. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non small-cell lung cancer. N Engl J Med 2004;350:351–60.
17. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.
18. Heon S, Johnson BE. Adjuvant chemotherapy for surgically resected non-small cell lung cancer. J Thorac Cardiovasc Surg 2012;144:S39–42.
19. Bae HM, Min HS, Lee SH, et al. Palliative chemotherapy for pulmonary pleomorphic carcinoma. Lung Cancer 2007;58:112–5.
20. Hong JY, Choi MK, Uhm JE, et al. The role of palliative chemotherapy for advanced pulmonary pleomorphic carcinoma. Med Oncol 2009;26:287–91.
21. Ushiki A, Koizumi T, Kobayashi N, et al. Genetic heterogeneity of EGFR mutation in pleomorphic carcinoma of the lung: response to gefitinib and clinical outcome. Jpn J Clin Oncol 2009;39:267–70.
22. Pelosi G, Scarpa A, Manzotti M, et al. K-ras gene mutational analysis supports a monoclonal origin of biphasic pleomorphic carcinoma of the lung. Mod Pathol 2004;17:538–46.
23. Italiano A, Cortot AB, Ilie M, et al. EGFR and KRAS status of primary sarcomatoid carcinomas of the lung: implications for anti-EGFR treatment of a rare lung malignancy. Int J Cancer 2009;125:2479–82.
24. Jiang X, Liu Y, Chen C, et al. The value of biomarkers in patients with sarcomatoid carcinoma of the lung: molecular analysis of 33 cases. Clin Lung Cancer 2012;13:288–96.
25. Fallet V, Saffroy R, Girard N, et al. High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta™ panel: exploring therapeutic targets. Ann Oncol 2015;26:1748–53.