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Pulmonary Carcinosarcoma: A Rare and Poor Prognosis Cancer–A Retrospective Analysis

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ABSTRACT

Pulmonary carcinosarcoma (PCS) is an uncommon and aggressive cancer, characterized by a combination of epithelial and sarcomatous tissue components. It is responsible for less than 1% of all lung tumors and usually affects older male smokers. However, the clinicopathological features and biological behavior of PCS remain insufficiently explored. This study aimed to shed light on these aspects. A total of eight patients with pathologically confirmed PCS were included in this retrospective study. The tumors varied in size, with diameters ranging from 3.5 cm to 21.5 cm. Six patients had central tumors, while the remaining two had peripheral lesions. Symptoms were largely dependent on the location of the tumor and included coughing, shortness of breath, and hemoptysis. Surgical resection was performed in seven patients, although PCS is known for its rapid progression and frequent metastasis, which results in a poor prognosis and limited survival, usually between 6 months and 1 year. The role of neoadjuvant and adjuvant chemotherapy-radiotherapy remains controversial, and there is no consensus on its effectiveness. Surgical resection of the lung is still considered the most appropriate treatment, but even with this intervention, survival rates are generally low. Given the rarity and challenging nature of PCS, further studies are needed to explore more effective treatment options for this cancer.

Keywords: Survival rate, Pulmonary carcinosarcoma, Pathology, PCS, Surgery, Prognosis

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Introduction

Pulmonary carcinosarcoma (PCS) is an exceptionally rare lung tumor, constituting only about 0.1% to 0.3% of all primary lung cancers [1-3]. The condition was initially documented by Kika *et al*. in 1908. In the most recent lung tumor classification by the World Health Organization (WHO) in 2021, PCS is placed within the category of sarcomatoid and pleomorphic carcinomas, which includes other tumor types such as giant cell carcinoma, pulmonary blastoma, and spindle cell carcinoma [4, 5]. This malignancy is characterized by a combination of two histological forms—epithelial and sarcomatous tissues [6, 7]. PCS is predominantly diagnosed in older males who have a history of smoking, typically around the ages of 60 to 70 years [8-10]. Common clinical symptoms include cough, chest discomfort, shortness of breath, fatigue, and unintentional weight loss, with the most frequent initial symptom being a persistent cough, found in 57% of patients [11].

The diagnosis of PCS is often made through routine chest imaging, with approximately 37.5% of cases being identified this way [12, 13]. The median size of the tumors at detection is approximately 6.2 cm, although this can range from 1.2 cm to 15.0 cm [14]. On imaging, PCS typically presents as either a solitary mass or a large opacity, which may be associated with obstructive pneumonitis, atelectasis, or large mass formation [15]. PCS can be divided into central and peripheral types [16, 17]. Central lesions tend to be more localized and grow at a slower rate, while peripheral tumors are more prone to early metastasis and exhibit broader invasiveness [18, 19].

Recent investigations have emphasized that PCS is most effectively diagnosed through its unique morphological features, confirmed with immunohistochemistry after surgical resection [19, 20]. In the early stages, the treatment of choice is typically complete surgical removal. For more advanced cases, palliative chemotherapy is often considered, though it generally yields limited success, and patients frequently succumb to the disease within a few months due to rapid progression [21, 22].

The clinicopathological features and biological behavior of PCS remain insufficiently explored. This study aimed to shed light on these aspects.

Materials and Methods

Study design

This retrospective research was conducted at Amsterdam University Medical Center (AUMC-VUMC) from 1990 to 2018, with approval from the medical ethics committees of the relevant departments: Pulmonary Medicine, Pathology, and Thoracic Surgery. Informed consent was obtained from all patients and their immediate family members before participation.

Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database and the pathology database at AUMC-VUMC using Dynamic SQL. The main endpoint of the study was patient mortality.

Inclusion and exclusion criteria

The study focused on adult patients diagnosed with PCS, excluding those with other types of lung cancer.

Study population

The study included eight patients diagnosed with PCS, all of whom underwent routine clinical evaluations, laboratory tests, and imaging studies, such as chest X-rays, CT scans, and PET scans. Additionally, a biopsy was obtained through bronchoscopy, and one patient with mediastinal lymphadenopathy underwent mediastinoscopy. The clinical analysis took into account patient characteristics including age, gender, presenting symptoms, diagnostic procedures, pathology findings, surgical interventions, and follow-up outcomes. A standard preoperative and postoperative TNM staging system was applied for all cases.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25, with a significance level set at a P-value of 0.05. Survival outcomes were analyzed using Kaplan–Meier methods, with factors such as tumor location, disease stage, and treatment approaches being examined.

Results and Discussion

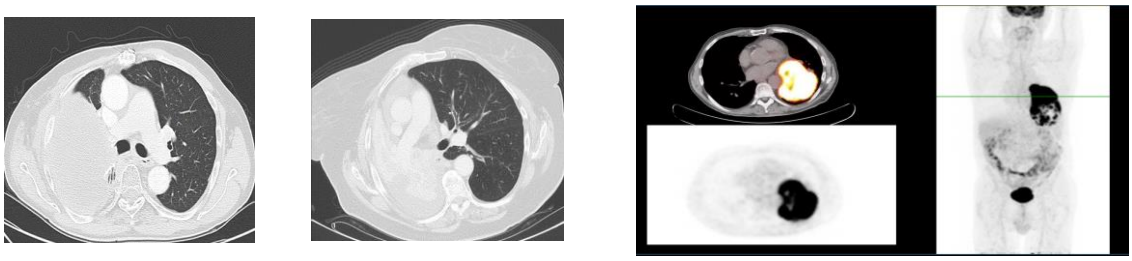
The cohort comprised eight patients diagnosed with PCS, consisting of five males and three females. All participants were smokers, and their ages ranged from 50 to 79 years. Cough and dyspnea were the most prevalent symptoms reported by the patients upon presentation.

In terms of tumor localization, six patients exhibited central lesions **(Figures 1a and 1b)**, while two had peripheral lesions **(Figure 1c)**. Tissue samples were collected before surgery in seven cases, with bronchoscopy being the primary diagnostic method for six patients **(Figure 2)**, and mediastinoscopy was employed for one. Only one patient received a postoperative diagnosis of PCS **(Table 1)**. Histologically, all tumors demonstrated a biphasic structure, with a close combination of both carcinomatous and sarcomatous components, as shown in **Figures 3a and 3b**.

Table 1. Characteristics of the patients with PCS tumors

Patient	Age (years)	Gender	Location	Diameter Radiologic (R) Macroscopic (M)
1	50	F	Left upper lobe (central)	8.5 × 8.2 cm (R)
2	65	M	Right upper lobe (central)	5.5 × 4.5 cm (R)
3	76	M	Left upper lobe (central)	3.6 × 3.5 cm (R)

4	72	M	Left lower lobe (peripheral)	13 × 9 × 6 cm (M)
5	70	M	Left lower lobe (peripheral)	21.5 × 14 × 13.5 cm (M)
6	60	M	Right upper lobe (central)	21 × 18 × 9 cm (M)
7	79	F	Right upper lobe (central)	9.5 × 7 × 7 cm (M)
8	64	F	Right upper lobe (central)	14 × 13 × 3.5 cm (M)



a) b) c)

Figure 1. a) chest CT scan reveals a sizable endobronchial tumor located in the right upper lobe of a patient diagnosed with PCS, b) chest CT scan depicts right upper lobe collapse accompanied by an ipsilateral mediastinal shift, caused by compression or blockage of the right upper lobe bronchus due to a central lung mass, and c) PET-CT scan shows the presence of a large peripheral tumor in the left lower lobe.

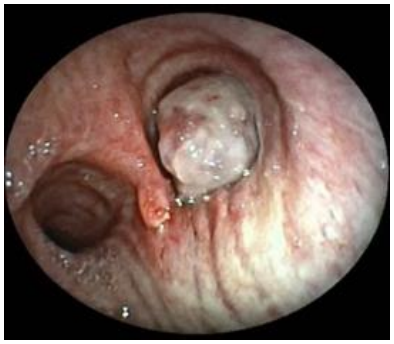
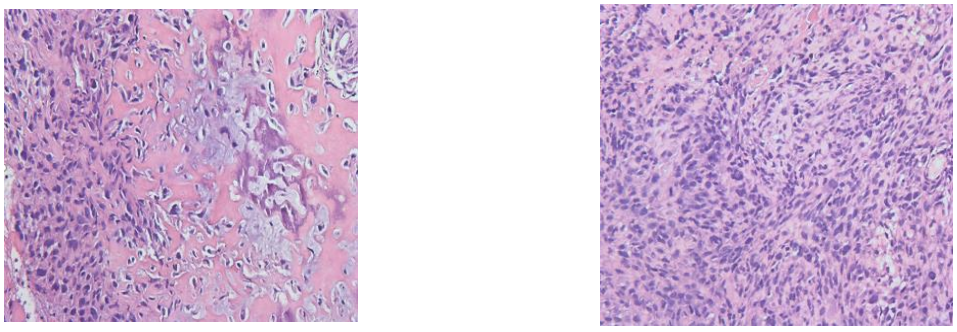


Figure 2. Bronchoscopy image displaying a significant endobronchial tumor blocking the right upper bronchus.



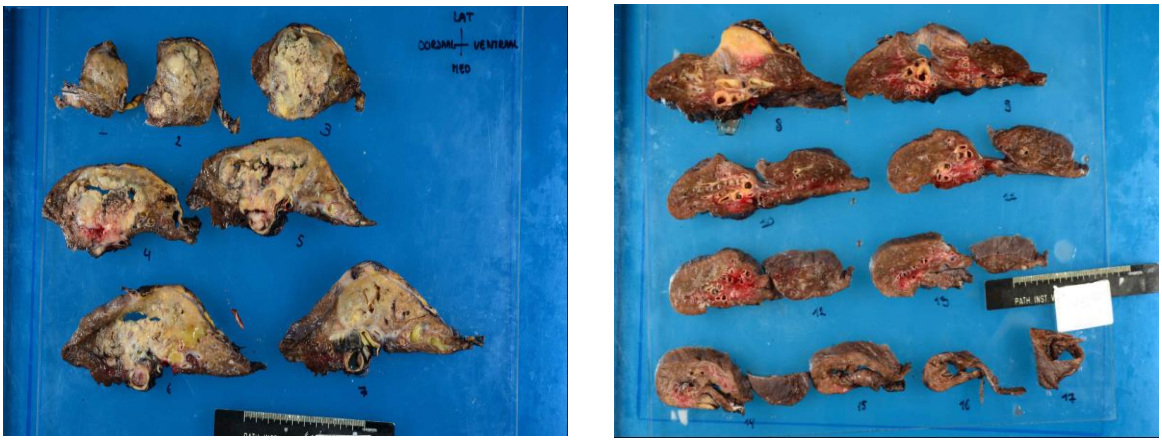
a) b)

Figure 3. Histological examination of a surgical lung biopsy sample: Both images (a, b) reveal a combination of sarcomatous and carcinomatous elements; the biphasic tumor features dense clusters of poorly differentiated epithelioid cells, exhibiting polymorphic and elongated hyperchromatic nuclei along with scattered mitotic figures; adjacent to this area, there is a distinct shift to a mesenchymal component that includes cartilage and osteoid formation.

A total of seven patients underwent complete resection, including six patients who had lobectomy and one who had pneumonectomy. Among the six lobectomy patients, five had upper and lower lobectomies **(Table 2)**. The tumors in all the patients were large solid masses, with sizes varying from 3.5 cm to 21.5 cm in diameter **(Figures 4a and 4b)**.

Table 2. Treatment strategies and follow-up data

Stage	Local/ Metastasis	TNM	Surgery/ Chemotherapy	Follow-up	Outcome
IV	Metastasis	T4 N3 M1	Chemotherapy	1 month	Dead
IB	Local	T2A N0 M0	Lobectomy	8 years	Dead
IB	Local	T2A N0 M0	Lobectomy	4 days	Dead
IIB	Local	T3 N0 MO	Lobectomy	7 days	Dead
IIIA	Local	T3 N1 MO	Lobectomy	6 months	Dead
IIIA	Local	T3 N1 M0	Lobectomy, then adjuvant chemotherapy	3 months	Dead
IIB	Local	T3 N0 MO	Pneumonectomy	4 months	Dead
IIIA	Local	T3 N1 M0	Neoadjuvant chemotherapy, then lobectomy	2 years	Alive



a) b)

Figure 4. Gross images display a sizable tumor with an uneven edge (a and b).

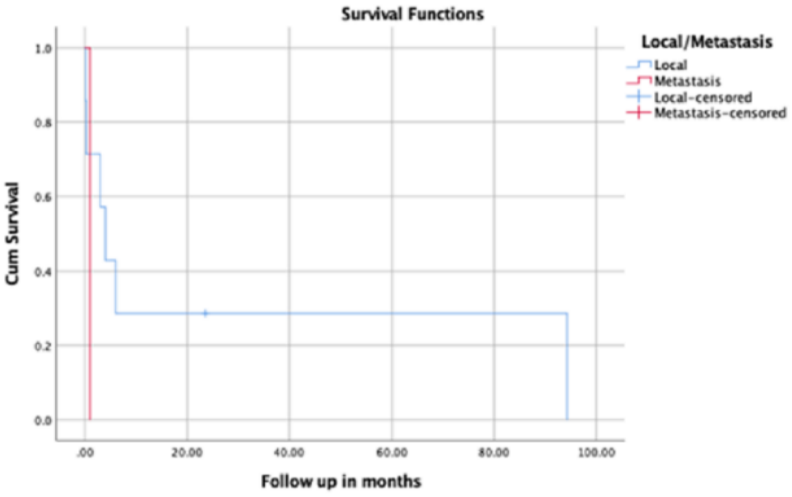
Of the seven patients who had complete surgical resection, only one remained alive at the time of writing. The other six patients passed away, with one surviving for eight years, three dying within a few months due to metastatic spread and cachexia, and 2 dying due to postoperative complications in the intensive care unit (ICU). Systemic chemotherapy is commonly used in advanced cases, particularly for stages III and IV. Unfortunately, chemotherapy did not show significant benefits for patients with PCS. One stage IV patient passed away two months after receiving a chemotherapy regimen including carboplatin, gemcitabine, and ifosfamide. Two patients with stage IIIA were treated with induction chemotherapy—one received it as adjuvant therapy, while the other underwent neoadjuvant chemoradiotherapy with carboplatin and etoposide. In addition, one patient was given neoadjuvant radiotherapy and another received immunotherapy.

Survival analysis of pulmonary carcinosarcoma using Kaplan–Meier method

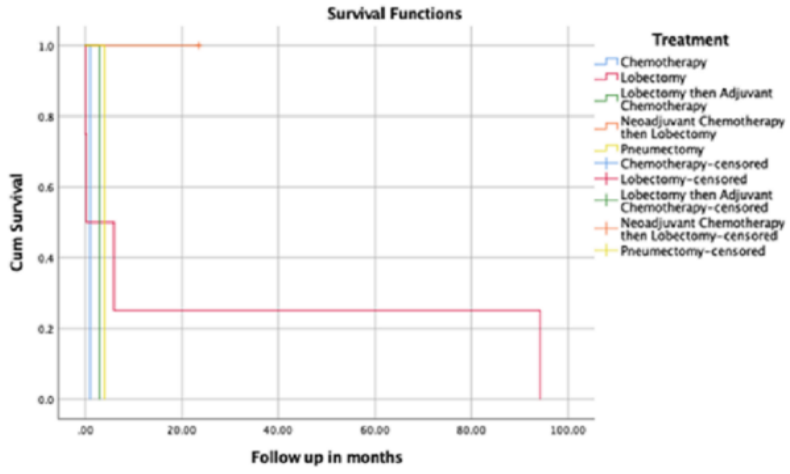
Figure 5a illustrates the survival curve for patients based on the tumor's location. Both localized and metastatic tumors were found to be linked with poor outcomes, with no significant survival difference observed between the two groups.

Figure 5b presents the survival curve relative to the treatments administered. The analysis revealed no treatment to be significantly more effective in improving patient survival.

Figure 5c displays the survival curve of patients according to the tumor stage. The stage of the tumor did not appear to influence survival outcomes in a statistically meaningful way.



a)



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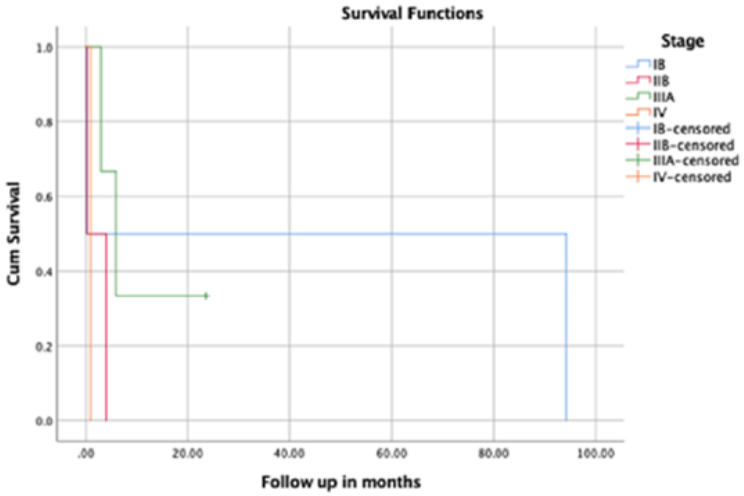

c)

Figure 5. a) Kaplan-Meier survival analysis indicating follow-up in days based on tumor location, b) Kaplan-Meier survival analysis showing follow-up in days concerning the type of treatment administered, and c) Kaplan-Meier survival analysis with follow-up in days according to the tumor stage.

Pulmonary carcinosarcoma (PCS) is a rare, aggressive malignancy that consists of both non-small cell lung carcinoma and sarcoma-like tissue, often containing elements from heterologous tissues [1, 4]. It represents 0.1% to 0.3% of all lung cancers [2, 3]. Typically, PCS is a large mass (> 5 cm), with some lesions exceeding 21 cm, and is known for its tendency to invade nearby structures such as the pleura, chest wall, diaphragm, and mediastinum [23]. In our study, the tumor sizes ranged from 3.5 cm to 21.5 cm. The patient cohort consisted mainly of males (5/8), aged 50 to 79 years, and all were smokers. Previous studies suggest that heavy smokers are at higher risk for PCS, with asbestosis often being a contributing factor [24].

PCS can occur in several organs, including the uterus, thyroid, breast, esophagus, and lungs [25]. The epithelial portion typically consists of squamous cell carcinoma or adenocarcinoma, while the sarcomatous portion may include rhabdomyosarcoma, osteosarcoma, or chondrosarcoma [3, 4, 26]. It is believed that both components originate from a shared stem cell, with carcinoma undergoing sarcomatoid transformation [27, 28]. Theories about PCS pathogenesis suggest several mechanisms, including (a) malignant transformation of hamartoma, (b) concurrent malignancy in both epithelial and stromal components, (c) changes in the cancer-derived stroma, (d) sarcomatous modifications of carcinoma, and (e) carcinomatous changes in sarcoma [29]. Immunohistochemical markers help identify the tumor components, such as p63 and p40 for squamous cell carcinoma, TTF-1 and keratin 7 for adenocarcinoma, and desmin and myogenin for rhabdomyosarcoma, or S100 for chondrosarcoma [4, 30]. The most commonly observed epithelial type was squamous cell carcinoma (46%), followed by adenocarcinoma (31%) and adenosquamous carcinoma (19%), while the sarcomatous elements were predominantly rhabdomyosarcoma, chondrosarcoma, and osteosarcoma [31]. Takeda *et al*. found squamous cell carcinoma to be the most frequent epithelial element in their study.

PCS can present in 2 locations: central endobronchial and peripheral. Koss *et al*. conducted an extensive study with 66 PCS patients, finding that 62% had central tumors, while 38% had peripheral lesions. In contrast, Sökücü *et al*. found that of six patients, 4 had peripheral tumors and 2 had central tumors [32], while Yazıcı *et al*. reported 85.7% of their cases were peripheral. In our study, six patients had central endobronchial tumors, and 2 had peripheral ones.

The most common presenting symptoms were cough and dyspnea. Depending on the tumor's location, symptoms vary. Peripheral tumors tend to be asymptomatic in the early stages, while central tumors are more likely to cause symptoms like cough, hemoptysis, and dyspnea. Symptoms in the peripheral type develop when adjacent structures such as the mediastinum or pleura are involved. PCS can also be associated with paraneoplastic syndromes, though specific manifestations are not well-documented. These may include systemic, dermatologic, renal, endocrine, hematologic, or neurological symptoms [33].

Diagnosing PCS preoperatively can be difficult due to the tumor's mixed histological components. Biopsies often reveal only one element, particularly with centrally located tumors, while peripheral tumors can be difficult to access for biopsy. As a result, many cases are diagnosed postoperatively [19, 32]. In contrast, our study found that seven out of eight patients were diagnosed before surgery, using bronchoscopy for six patients and mediastinoscopy for one.

Metastasis is common in PCS, with the lymph nodes being the most frequently affected site, followed by the kidneys, bones, liver, and brain [31]. In this study, three patients had metastases: two with distant metastases and one with pleural metastasis. Previous research shows that metastatic lesions are typically either carcinomatous (50%) or sarcomatous (40%), with 10% showing both components [19].

The primary treatment for PCS at an early stage is surgical resection, often combined with adjuvant chemotherapy for higher-risk stages (IB, II, and IIIA). Palliative chemotherapy is used in more advanced cases. However, prior studies have demonstrated poor responses to chemotherapy. Liang *et al*. reported that chemotherapy regimens, including platinum-based treatments and combinations with doxorubicin or ifosfamide, did not improve survival in their cohort of 33 patients [2]. Similarly, Caviglia *et al*. found chemotherapy to be poorly effective. In a case reported by Ito *et al*., five patients who received palliative chemotherapy showed no clinical benefits, and Langer *et al*. noted partial remission after six cycles of cisplatin and doxorubicin. Elalami *et al*. [34] reported no benefit from palliative chemotherapy with cisplatin and docetaxel in a stage IV patient, who died three months after diagnosis. In our study, 3 patients received chemotherapy. One with stage IV PCS underwent palliative chemotherapy with carboplatin, gemcitabine, and ifosfamide for four cycles but showed no response, passing away one month later. Two patients with stage IIIA PCS received induction chemotherapy. One underwent cisplatin, docetaxel, and nivolumab with no response and died three months after treatment, while the other had

neoadjuvant chemoradiotherapy with carboplatin and etoposide, showed partial response, and later had a right upper lobectomy, remaining alive at the time of the study.

Emerging treatments include nivolumab for PCS patients with PD-L1 positivity [35, 36], and molecular targeting strategies focused on pathways like EGFR, K-RAS, and ALK may provide further treatment options in the future [22].

PCS has a generally poor prognosis, with median survival times of 9 to 12 months after curative surgery [26, 37], and fewer than 10% of patients surviving beyond two years. In our research, 7 patients underwent complete resection, but only one remained alive at the time of the study. Factors such as tumor size and lymph node involvement are known to negatively impact survival.

The main limitation of this study is the small sample size, as PCS is rare. Future multicenter studies should focus on increasing the number of patients to achieve more comprehensive findings.

Conclusion

Pulmonary carcinosarcoma (PCS) is a rare and highly malignant tumor, characterized by its aggressive nature and unfavorable prognosis. Survival rates for PCS, even following complete surgical removal, are similar to those observed in other types of lung cancers. Furthermore, there is insufficient evidence to support the effectiveness of chemotherapy in extending survival, as advanced PCS typically shows minimal response to such treatments.

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