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Clinical characteristics and prognosis of pulmonary pleomorphic carcinoma: retrospective analysis of 57 patients

Pulmoner pleomorfik karsinomun klinik özellikleri ve prognozu: 57 hastanın retrospektif analizi

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ABSTRACT

Background: This study aims to evaluate clinical characteristics and prognosis of pulmonary pleomorphic carcinoma.

Methods: The study included 57 patients (54 males, 3 females; mean age 60.4 years; range 33 to 75 years) operated for pleomorphic carcinoma. The patients who underwent surgery with the diagnosis of pleomorphic carcinoma in our clinic between 1999 and 2009 were recruited to the study. Datas were recorded retrospectively from the patient files.

Results: Of all patients, 54 were smokers (mean 49.9 packets/year). Most common symptoms were hemoptysis and cough, and 51 patients were asymptomatic. All patients' diagnoses were confirmed postoperatively as pleomorphic carcinoma. Surgical approaches applied were five parenchyma sparing resections, 35 lobectomies, seven bilobectomies, and one thoracoscopic biopsy. Of epithelial components, 28 were adenocarcinomas, 15 were epidermoid carcinomas, and six were large cell carcinomas; whereas of sarcomatoid components, 28 had spindle cells, 22 had giant cells, and seven had a mix of spindle and giant cells. At the end of the follow-up period, 28 deaths were recorded. Mean survival was 62 months.

Conclusion: Despite surgery and adjuvant chemoradiotherapy, pleomorphic carcinoma is associated with poor prognosis because of frequent distant metastasis. Staging seems to be an important prognostic factor, particularly in N_0 patients.

Keywords: Pleomorphic carcinoma; prognosis; surgery.

ÖZ

Amaç: Bu çalışmada pulmoner pleomorfik karsinomun klinik özellikleri ve prognozu değerlendirildi.

Çalışma planı: Çalışmaya pleomorfik karsinom nedeni ile ameliyat edilen 57 hasta (54 erkek, 3 kadın; ort. yaş 60.4 yıl; dağılım 33-75 yıl) dahil edildi. Kliniğimizde 1999-2009 yılları arasında pleomorfik karsinom tanısıyla opere edilen hastalar çalışmaya alındı. Tüm veriler hasta dosyalarından retrospektif olarak kaydedildi.

Bulgular: Hastaların 54'ü sigara içmekte (ortalama 49.9 paket/yıl) idi. En yaygın semptomlar hemoptizi ve öksürük idi ve 51 hasta asemptomatik idi. Tüm hastaların tanısı pleomorfik karsinom olarak ameliyat sonrası doğrulandı. Uygulanan cerrahi yaklaşımlar beş parenkim koruyucu rezeksiyon, 35 lobektomi, yedi bilobektomi ve bir torakoskopik biyopsi idi. Epitelyal komponentlerin 28'i adenokarsinom, 15'i epidermoid karsinom, altısı büyük hücreli karsinom iken, sarkomatoid komponentlerin 28'inde iğsi hücreler, 22'sinde dev hücreler, yedisinde ise iğsi ve dev hücrelerin karışımı var idi. Takip süresi sonunda 28 ölüm kaydedildi. Ortalama sağkalım 62 ay idi.

Sonuç: Cerrahi ve adjuvan kemoradyoterapiye rağmen, pleomorfik karsinom sık uzak metastaza bağlı olarak kötü prognoz ile ilişkilendirilmektedir. Evreleme özellikle N_0 hastalarda önemli bir prognostik faktör olarak gözükmektedir.

Anahtar sözcükler: Pleomorfik karsinom; prognoz; cerrahi.

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Pleomorphic carcinoma (PC), which constitutes 0.1-0.4% of all malignant lung tumors, is a rare epithelial tumor with a poor prognosis.[1-3] The 2004 World Health Organization (WHO) lung tumor histological classification grouped PC with spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma in the sarcomatoid carcinoma category.[4] This group of tumors has sarcoma or sarcoma-like (spindle and/or giant cell) differentiation components as well as poorly differentiated non-small cell lung carcinoma (NSCLC). Pulmonary PC is defined as poorly differentiated, squamous cell carcinoma, adenocarcinoma, or large cell carcinoma which contains a component of spindle or giant cells and has a sarcomatoid tumor component of at least 10%.[5] Besides the lungs, PC can originate from the larynx, oral cavity, thyroid, breast, pancreas, kidney, or urinary bladder, but the same poor prognosis also holds true for these locations.[6]

The rarity of pulmonary PC makes it confusing to classify and difficult to diagnose.[1] Before 1999, this type of tumor was classified as a variant of squamous cell carcinoma,[7] but beginning in that year, it was classified in the carcinoma group along with pleomorphic, sarcoma, or sarcoma-like elements. Then in 2004, the WHO reclassification took place, and PC was included as one of the five elements of sarcomatoid carcinoma.[4] After this detailed pathological description was made, the number of PC diagnoses began to increase. The patients included in this study were treated during the period after the classification of the first sarcomatoid element in 1999, but the staging was done according to the 2009 TNM classification of malignant tumors.[8]

In the initial years, PC constituted from 0.1 to 0.4% of all malignant lung tumors,[2,3] but since the modifications in the classification and the resolution of the pathological diagnostic difficulties, there has been an increase in the incidence rate (1.3-4%).[9-11]

After the 1999 WHO classification, the difficulty in defining PC histopathologically persisted in spite of the publication of a few PC series in the international literature. In addition, even though the 2004 PC classification revision received universal acceptance, the clinical relevance and the behavior of the tumor remains uncertain.

In this retrospective cross-sectional study, we analyzed patients with a pathological diagnosis of PC with a goal toward determining the clinicopathological characteristics of these patients and, in particular, the prognostic factors related to the their survival.

PATIENTS AND METHODS

Initially, we screened the patients who had undergone surgical resection for primary lung carcinoma in the thoracic surgery department of our hospital between January 1999 and December 2009. Then we screened the 2,854 patients for whom the diagnosis had been postoperatively confirmed as primary PC, and 57 of these (54 males, 3 females; mean age at diagnosis 60.4 years; range 33 to 75 years) were enrolled in this study. A retrospective analysis of the patients' demographics and disease characteristics, including age and gender along with the presenting symptoms, smoking habits, diagnostic approach, disease stage, and survival rates was then carried out. All of this data is shown in Table 1. Furthermore, this study was approved by the local ethics committee.

Metastatic disease is routinely detected by brain computed tomography (CT), abdominal CT, and a bone scan. However, for the last four years at our facility, we have been using positron emission tomography-computed tomography (PET-CT). All of the patients underwent preoperative pulmonary function tests, and cardiac evaluations were performed for those with a history of cardiac disease as well as those who were older than 50 years of age. No patients received preoperative chemotherapy.

A preoperative diagnosis of primary lung cancer was obtained via sputum cytology and/or a transbronchial or transthoracic needle biopsy in 49 of the 57 patients. However, a diagnosis of PC was only made after performing a surgical resection.

Standard anesthesiology procedures were used in all of our cases. Ventilation was always given via the use of a double-lumen tube, and a cervical mediastinoscopy was performed before the major surgery to evaluate the mediastinal lymph nodes. A subsequent surgical resection was carried out for those patients with a negative frozen result for nodal involvement. Video thoracoscopic surgery (VATS) was used in only one patient (2%) to excise a solitary pulmonary nodule. A standard posterolateral thoracotomy incision through the fifth intercostal space was used for the remaining patients.

All of the removed specimens were formalin-fixed and paraffin-embedded. For each specimen, 4-5 μm thin slices were taken and stained with hematoxylin and eosin (H-E). We also re-evaluated all of the tumor cases in our series microscopically. For the squamous cell carcinoma component, the diagnosis was confirmed by the presence of

Table 1. Patient characteristics

Characteristics	n	%	Median	Range (years)	*p*
Gender					0.343
Males	54	94.7			
Females	3	5.7			
Age			60.4	33-75	
Smoking status					0.266
Smokers	54	95			
Non smokers	3	5			
Symptoms					<0.05
Hemoptysis	27				
Cough	24				
Chest pain	22				
Other	21				
Asymptomatic	6				
Median tumor size (cm)			6.6	2.2-12	
Non-small cell type					0.599
Adeno carcimoma	36	63			
Squamous cell carcinoma	15	26			
Large	6	11			
Stage					
1	7	12.3			
2	31	54.4			
3	19	33.3			

keratinization and/or intercellular bridges. For poorly differentiated tumors, the diagnosis was supported by immunohistochemical positivity for cytokeratin 5/6, and adenocarcinoma was confirmed in patients if they had solid tumors with glandular, acinar, papillary, or bronchioloalveolar architecture who also a positive stain for mucin. Furthermore, in low differentiated tumors, the diagnosis was verified by thyroid transcription factor 1 (TTF-1) and/or napsin A positivity. Tumors with no morphological or immunohistochemical differentiation were reported as large cell carcinoma. In these tumors, epithelial differentiation was demonstrated by pancytokeratin and the epithelial membrane antigen (EMA). Additionally, a tumor can be reported as PC when the spindle cell and/or giant cell component was greater than 10%. No heterologous elements such as cartilage, bone or skeletal muscle were observed in any of the sarcomatoid components.

We also studied the impact of the TNM staging of the epithelial components (adenocarcinoma, epidermoid carcinoma, and large cell carcinoma) on survival. Postoperative recurrences were screened by CT and/or PET-CT, and if recurrence was detected, the diagnosis was confirmed by a pathological evaluation of the biopsy specimens. Except for N_0 disease, all of the patients received adjuvant chemotherapy. Local advanced disease or patients with N_{1-2} nodal metastasis were given cisplatin-based chemotherapy, whereas those with a T_{3-4} tumor and/or N_2 nodal involvement received radiotherapy.

Statistical analysis

Statistical analyses were carried out using the SPSS for Windows version 15.0 statistical software program (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and categorical variables as frequencies and percentages. A chi-square test was used to determine the associations between categorical variables, and the differences between the groups were determined using the Kruskal-Wallis test. In addition, the Kaplan-Meier method was used to estimate the probability of survival, and significance was assessed via the log-rank test. Moreover, the effects of age, gender, smoking, and tumor size on survival were evaluated using Cox regression model. A *p* value of less than 0.05 was considered to be significant.

RESULTS

The most common presenting symptoms were hemoptysis in 27 (47%) patients, cough in 24 (42%)

more, and chest pain in 22 (39%) others. Additionally, six patients were asymptomatic, and four had an incidental roentgenogram finding of a pulmonary nodule or mass. Fifty-four patients (95%) were current or ex-smokers, and the mean smoking duration was 49.9 packs/year (range 0-120 packs/year). The patients' clinical characteristics are shown in Table 1.

Chest CT and a chest X-ray revealed 36 (63%) lesions in the right lung and 21 (37%) in the left lung. In addition, the cancerous lesions were peripherally located in 45 patients (79%) and centrally located in 12 others (21%). Thirty-nine (68%) were found in the upper lobe and 18 (32%) in the lower lobe. Furthermore, in 51 patients, the tumoral lesion was determined to be either a mass or a pulmonary nodule, whereas in six others, it was identified as either a ground glass opacity or pulmonary consolidation. Thoracic wall invasion with no extrathoracic metastasis was present in 10 patients, and only five had suspicious N_2 disease on PET-CT.

In six patients, carcinoma cells without spindle and/or giant cells were identified. Four of these were diagnosed as squamous carcinoma and two with adenosquamous carcinoma.

Diagnosis via a transbronchial needle biopsy was performed on six patients with NSCLC and in two with suspicious malignancies. In addition, 18 others underwent transthoracic needle aspiration, with 10 being diagnosed with NSCLC, 12 with squamous cell carcinoma, and eight with adenosquamous cell carcinoma. Five patients were also found to have suspicious malignancies while no diagnosis was recorded for three others. The microscopic pathology sections of the patients with adenocarcinoma and squamous cell carcinoma are shown in Figure 1.

Regarding the types of surgery, six patients (11%) with compromised pulmonary function and a peripherally located nodule underwent a parenchyma-sparing resection (either a segmentectomy or wedge resection). Furthermore, 35 (61%) lobectomies were performed along with nine (16%) pneumonectomies, and seven (12%) bilobectomies. *En-bloc* removal of the tumoral mass from the invaded rib (between 1 and 4 ribs) was carried out on 10 PC patients with thoracic wall involvement (9 upper lobectomies and 1 upper bilobectomy). Apart from the patient for whom the VATS approach was utilized, all of the other patients underwent complete ipsilateral mediastinal lymph node dissections (nodal stations 2, 4, 5, 6, 7, 8, and 9).

The mean tumor size of the pathological specimen was 6.6 cm (range 2.2-12 cm). After analyzing the epithelial component, 36 (63%) were found to be adenosquamous carcinoma. Moreover, 15 (26%) had epidermoid carcinoma and six (11%) large cell carcinoma. In terms of the sarcomatoid component, 28 (49%) of the tumors were identified as spindle cell, 22 (39%) as giant cell, and seven (12%) as a combination of the two. The distribution of the cases according to the 2009 TNM classification is shown in Table 2.

Thirty-day mortality was noted in three patients, with two dying from myocardial infarction and one from postoperative ileus. The mean follow-up period for the study was 24.4 months (range 1-120 months). During that time, 18 patients (31.6%) died from locoregional or extrathoracic recurrence, and seven (12.3%) died from reasons unrelated to lung disease. Most of these 18 patients had multiple metastases, with the most common sites of recurrence being the brain, lungs, and bones.

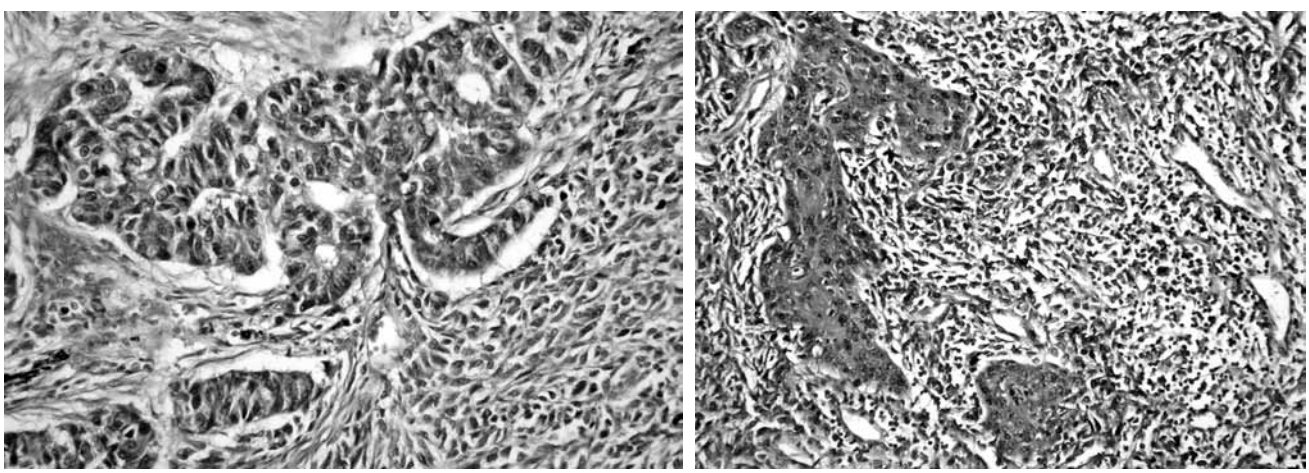

Figure 1. Microscopic pathological sections showing the adenocarcinoma with spindle cell carcinoma on the left (H-E x 200) and the squamous cell carcinoma with spindle cell carcinoma on the right (H-E x 100).

Table 2. Distribution according to the 2009 TNM classification

	Subgroup	n	*Total*
Stage 1			
1a	$T_{1b}\,N_0\,M_0$	2	7
1b	$T_{2a}\,N_0\,M_0$	5	
Stage 2			
2a	$T_{2b}\,N_0\,M_0$	8	31
	$T_{2a}\,N_1\,M_0$	5	
2b	$T_{2b}\,N_1\,M_0$	2	
	$T_3\,N_0\,M_0$	16	
Stage 3			
3a	$T_{2a}\,N_2\,M_0$	3	19
	$T_{2b}\,N_2\,M_0$	2	
	$T_3\,N_1\,M_0$	3	
	$T_3\,N_2\,M_0$	7	
	$T_4\,N_0\,M_0$	2	
	$T_4\,N_1\,M_0$	1	
3b	$T_4\,N_2\,M_0$	1	

The remaining 29 patients (51%) were alive and disease-free for a mean period of 41 months. The median survival for those with stage 1 disease was 64 months while it was 43 months for those with stage 2 and 49 months for those with stage 3. Moreover, the five-year survival rates for the patients with stage 1, stage 2, and stage 3 disease were 86%, 39%, and 37%, respectively. We also found that those with stage 1 disease had a better prognosis than those with stage 2 and stage 3; however, the difference was not statistically significant (p=0.183). In terms of staging, the overall five-year survival rate was 42.3%, with a mean survival of 60 months (min-max: 43-76, median:62 months) (Figure 2).

Univariate analysis showed that age and tumor size were statistically significant factors that affected survival. We also noted that as the age of the patient or the tumor size increased, the survival rate decreased (p=0.043 and p=0.024).

The information regarding smoking, tumor size, and staging distribution was similar among the cancer subgroups. For example, the mean survival and five-year survival rates for the adenocarcinoma group were 60 months and 41% while for the squamous cell carcinoma group, they were 39 months and 49% and for the large cell carcinoma group, they was 30 months and 33%, respectively. Furthermore, we found no difference in the survival between the various staging groups (Table 3, Figure 3).

Adjuvant chemotherapy was performed on six patients with N_1 cancer while adjuvant chemotherapy + radiotherapy was performed on 28 patients with N_2, T_3, T_4 carcinoma. Additionally, eight patients refused additional therapy.

DISCUSSION

The 42.3% five-year survival rate and 62-month median survival rate in this study signify that the

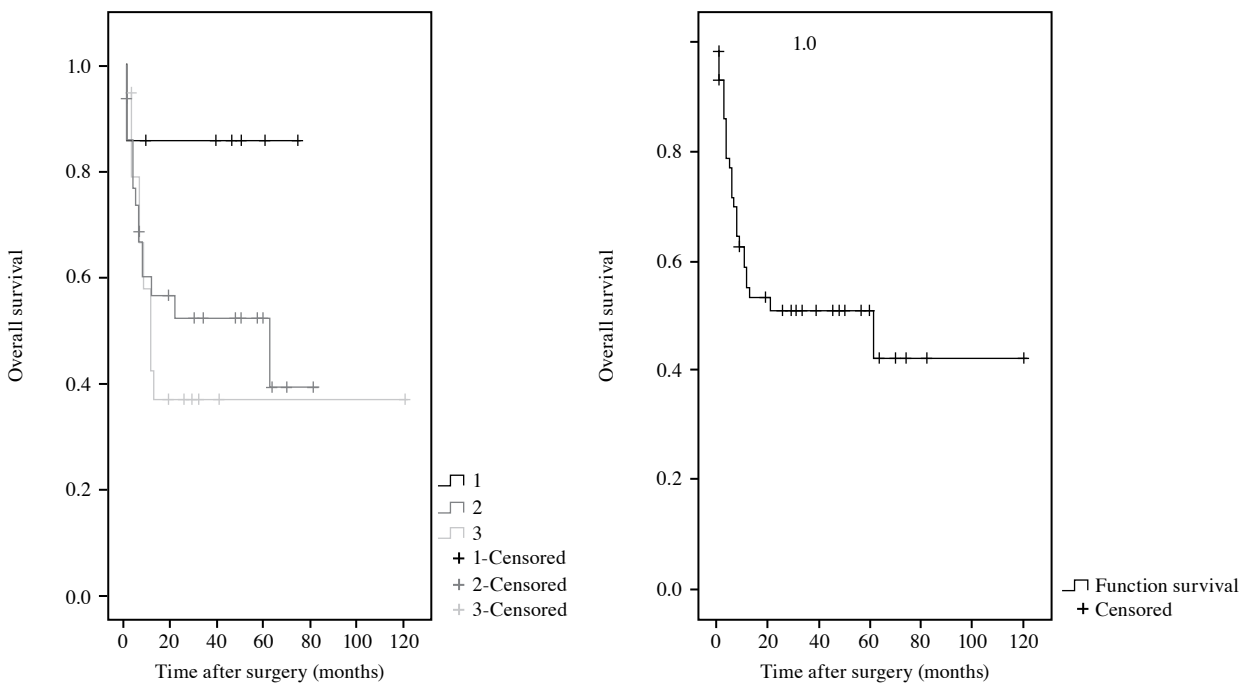

Figure 2. Between-stage survival and overall survival rates of the 57 patients.

Table 3. Survival figures comparing the epithelial and sarcomatoid components of pleomorphic carcinoma

Epithelial component	Sarcomatoid component	Total	Five-year survival (%)	Mean survival (months)	Overall five-year survival (%)
Adenocarcinoma	Spindle cell	13	39	49	41
	Giant cell	20	32	42	
	Spindle + giant cell	3	67	57	
Epidermoid carcinoma	Spindle cell	10	56	44	49
	Giant cell	1	100	19.5	
	Spindle + giant cell	4	25	18	
Large cell carcinoma	Spindle cell	5	40	34	33
	Giant cell	1	0	11	

survival rate of patients with PC is not lower than that of those with non-PC. We also found that age and tumor size appear to be important prognostic factors and that the demographic and clinicopathological features of our patients were similar to what has previously been reported in the literature.

In terms of demographic features, we had a higher rate of male predominancy in our study than in earlier studies.[12] Fishback et al.[3] reported a male-female ratio of 2.7:1 and Mochizuki et al.[13] reported a ratio of 4.4:1. In our study, the male-female ratio was actually 18:1, but this could possibly be attributed to lower smoking rates of females in our country.[14] Although a very few reports associated asbestos with PC, the primary factor in many patients is smoking,[3,15] with most PC patients being heavy smokers.[3,16]

Fishback et al.[3] also reported that their patients had a diagnostic age of 62 years; while Mochizuki et al.[13] determined that theirs had a diagnostic age of 67 years. In our study, the mean age was 60.4 years.

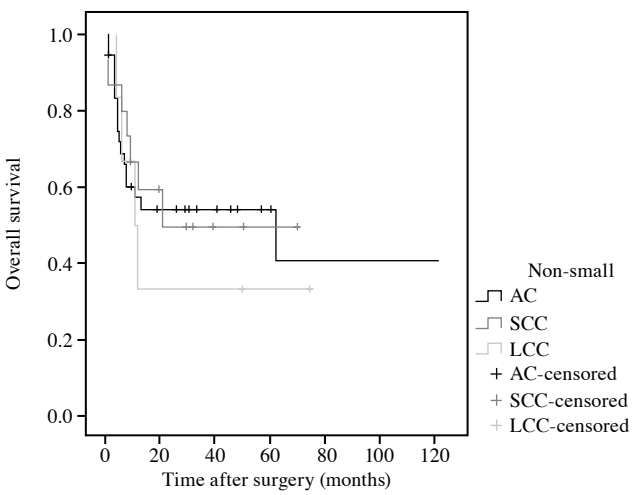

Figure 3. Overall survival rate of the epithelial component subgroup.

Most PC patients have nonspecific symptoms. Some studied have reported that patients with a centrally located tumor present with a cough, hemoptysis, progressive dyspnea, fever, and recurrent pneumonia, whereas those with peripheral tumors have pain as the main symptom due to the early pleural and chest wall invasion.[9,11,17] The biphasic component and tendency of PC to be located peripherally makes diagnosis via cytology or small tissue biopsies difficult.[10] Furthermore, due to sampling issues and histological heterogeneity, the diagnosis of virtually all sarcomatoid carcinomas requires a surgical specimen.[18] While the pathological findings of the patients in our study with carcinomatous or sarcomatous components were obtained via preoperative diagnostic methods, all of the patients in our series were diagnosed with PC after surgery.

Previous reports revealed that 68% of PC tumors were located in the upper lobe while 79% were centrally located,[3,9,11] and Kim et al.[19] found that 86% of their adenocarcinoma cases and 100% of their large cell carcinoma cases were located peripherally. In addition, they determined that 100% of those with epidermoid carcinoma had centrally located tumors. In our series, we found that 89% of the adenocarcinoma and 67% of the large cell carcinoma were located peripherally and that 60% of the epidermoid carcinoma was centrally located. Therefore, our findings were consistent with these other studies.

Several studies indicated that the epithelial component of PC was composed of 36-49% of patients with adenocarcinoma, 6.4-19% with epidermoid carcinoma, and 35-57% with large cell carcinoma.[3,9,11,17] In our study, nearly two thirds of the epithelial carcinomas were identified as adenocarcinoma, which was consistent with past findings. Furthermore, the sarcomatoid component distribution in previous studies was as follows:

29-38.5% spindle cell, 20-50% giant cell, and 14-51% a combination of the two,[3,11,17] which were 49%,39% and 12%, respectively in our study.

Because the pathological diagnoses of the patients in our series were verified after surgery, none of the resectable patients had neoadjuvant treatment. Moreover, to date, no chemotherapeutic regimens for PC have been established, and conventional cancer.[20] In addition, a preoperative mediastinoscopy was performed only in the patients who had mediastinal lymphadenopathy larger than 1 cm on thoracic CT scans and/or high maximum standardized uptake value (SUVmax) involvement on the PET-CT scans.

In their study consisting of 20 PC patients, Raveglia et al.[21] performed four pneumonectomies, 14 lobectomies, and two segmentectomies, whereas Fishback et al.,[3] performed surgical resections on 57 of their 78 patients (10 wedge resections, 10 pneumonectomies, 37 lobectomies, and two segmentectomies). According to this data, lobectomies and pneumonectomies seem to be the most preferred surgical approaches for PC. Moreover, when taking into consideration the findings of Yamamato et al.[22] who reported the highest survival rates for PC patients, curative resection may indeed be an important prognostic factor. However, it did not seem to affect the prognoses in our study.

The tendency of PC to metastasize is similar to that of other malignant epithelial tumors.[9] However, rare metastasis to the gastric and jejunum has been reported,[17] and the rate of the distant metastasis that occurred in 25 of our patients was similar to what had been previously. Mochizuki et al.[13] studied the overall survival and median survival rates among the three epithelial component subgroups and found that the five-year survival and median survival rates for adenocarcinoma were 41.5% and 34.9 months respectively, whereas they were 22.7% and 37.2 months for epidermoid carcinoma, and 39.1% and 8.6 months for large cell carcinoma.[17] In our study, the rates were 41% and 60 months for adenocarcinoma, 49% and 39 months for epidermoid carcinoma, and 33% and 30 months for large cell carcinoma.

Even though PC with both epithelial and sarcomatoid components has a better prognosis than that of tumors with only spindle or giant cell components, it is generally much more aggressive and its prognosis is significantly poorer than for patients with NSCLC.[23] The mean survival time has been reported as between 7.1 and 22.8 months[3,11,13,17,21,22,24,25] for PC with a five-year survival rate of 20.3% for adenocarsinoma, 16.8% for epidermoid carcinoma, and 12.1% for large cell carcinoma.[25] Our five-year survival, mean survival, and median survival figures were 2.3%, 60 months, and 62 months, respectively. A comparison of our results with those of previous studies is summarized in Table 4.

The high rate of survival in our study can be attributed to a variety of factors. First, we performed mostly lobectomies and pneumonectomies, which many consider to be curative resections. Although we found no statistically significant differences associated with these two procedures, we believe that PC may act in a potentially aggressive manner unless the tumor is partially resected. In addition, in previous series focused on heterogenous groups of patients diagnosed with sarcomatoid lung cancers, so there were relatively small numbers of PC patients. However, in our study, we specifically focused on the characteristics of patients with PC, and to the best of our knowledge this is the largest series to date that contains only PC tumors.

The main difference between our study and previous studies was that we used both the 2004 WHO classification,[4] which is based on a histological typing of lung tumors, and the 2009 TNM staging.[10] We believe that, by using the new TNM classification, staging of the disease can be done more correctly than the past. Mochizuki et al.[13] found that the presence

Table 4. Comparison between our study and previous studies

	Patient number (year)	Male/female	# of smoking (%)	Diagnosis	Five-year survival (%)	Median survival (months)	Prognostic factors
Fishback et al.[3]	78 (20)	57/21	96	Surgery, biopsy	10	10	Stage, N, size
Rossi et al.[11]	75 (17)	68/7	92	Surgery	NR	19	Stage
Raveglia et al.[21]	20 (4)	14/6	80	Surgery	20	8	N
Venissac et al.[24]	39 (15)	29/10	NR	Surgery	33	11	Size, DFI
Yuki et al.[25]	45 (21)	41/4	84	Surgery	39.2	NR	NR
Yamamoto et al.[22]	21 (8)	18/3	90	Surgery	80	NR	N, CR
Mochizuki et al.[13]	70 (28)	57/13	81	Surgery	36.7	22.8	Stage, N, MN
Ito et al.[17]	22 (4)	19/3	81.8	Surgery, autopsy, TBB	NR	7.1	Stage
Our study	57 (11)	54/3	95	Surgery	42.3	62	Size, age

N: Nodal involvement; NR: Not reported; DFI: Disease-free interval; CR: Curative resection; MN: Massive necrosis; TBB: Transbronchial biopsy.

of massive coagulation necrosis, stage, and nodal involvement were prognostic factors in their patients, whereas Venissac et al.[24] determined that the primary factors were size and the disease-free interval. In our study, univariate analysis identified age and tumor size as the prognostic factors, and we noted that patients stage 1 tumors had a longer five-year survival rate than those with stage 2 and stage 3 tumors.

Yamato et al.[22] found a five-year survival rate of 80% in their series that consisted of 21 patients. When compared with the studies mentioned in Table 4, the five-year and the median survival rates in our study is the second high results after Yamamoto's study.

Conclusion

Although malignancy may be detected preoperatively in patients with PC, it is primarily diagnosed via a pathological examination of the surgical specimen. These tumors are generally large and peripheral in nature and frequently affect elderly males who smoke. They also have a heterogeneous morphology, and these patients have a worse prognosis than those with NSCLC. The epithelial and sarcomatoid components as well as the tendency toward a peripheral location can make a preoperative diagnosis quite difficult, and staging seems to be the major diagnostic factor that affects the prognosis. We hope that this study will lead to future international studies related to the formation of acceptable surgical algorithms and methodological strategies related to this biphasic tumor.

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Declaration of conflicting interests

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