Original Article

Clinicopathological factors influenced the prognosis of surgically resected pulmonary pleomorphic carcinoma

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Background: Pulmonary pleomorphic carcinoma has made an unfavorable prognosis because of its properties of resisting radiation and chemotherapy, and its aggressive growth. The correlation between clinicopathological factors and prognosis about pulmonary pleomorphic carcinoma patients who received its surgical resection has not been clearly identified.

Methods: We retrospectively investigated the clinical records of 24 pulmonary pleomorphic carcinoma patients who had a surgical resection from January 2004 to December 2013 at our institute. We examined the correlation between their clinicopathological factors and therapeutic effects including their prognosis.

Results: The median follow up time was 2.3 years. The 5-year survival was 54.7% and the 5-year progression free survival was 52.4%. In comparison with other tissue types of lung cancer, the prognosis was not so poor even taking into consideration the survival curve including several progression stages. We analyzed the 21 clinicopathological factors in order to clarify the factors connected with the prognosis and disease progression. As a result, we found that both vascular invasion evaluated by immunohistochemistry and lymph node metastasis were connected closely with the overall survival. We found another strong link between the tissue type of epithelial components, vascular invasion evaluated by immunohistochemistry and lymph nodal metastasis with the progression free survival.

Conclusions: Pulmonary pleomorphic carcinoma patients with lymph node metastasis and vascular invasion had worse prognosis after their surgical resections. We have to find an effective chemotherapeutic drug or molecular targeted drug.

Keywords: Pulmonary pleomorphic carcinoma; lymph node metastasis; vascular invasion

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Introduction

Pulmonary pleomorphic carcinoma (PC) is a rare pulmonary histopathological type of primary lung cancer occupying about 0.1–0.4% (1). In 1999, WHO defined PC is a poorly differentiated non-small cell lung carcinoma (NSCLC) namely a squamous cell carcinoma, adenocarcinoma, or undifferentiated non-small cell carcinoma that contains at least 10% spindle and/or giant cells or a carcinoma consisting only of spindle and giant cells (2). According to the WHO report, PC makes an unfavorable prognosis because of its properties of resisting radiation and chemotherapy, and its aggressive growth (3-6). Since the studies of patients with PC was small and rare, the factors affecting their survival after having the pulmonary

resection for PC and its clinicopathological characteristics are still undiscovered.

This study aims at improving the understanding of the PC and exploring an adequate therapeutic strategy. Here we examined the correlation between clinicopathological factors and prognosis about 24 pulmonary PC patients who had surgical resection at our hospital and reviewed the previous reports of pulmonary PC.

Methods

We reviewed the past medical records of our institute, Nagoya City University Hospital. We operated 926 cases of NSCLC from January 2004 to December 2013. Out of those 926 patients, 24 (2.6%) were diagnosed as pulmonary PC. We closely examined the 24 cases in order to find the clinicopathological features of PC. The study was approved by the Institutional Review Board of Nagoya City University Hospital (No. 48), and a written consent was obtained each patient to use their clinicopathological data for research.

Since a diagnosis of PC before the surgery was quite difficult, most cases were diagnosed after a surgical resection. In our cases, one case was diagnosed as PC, 4 cases as adenocarcinoma, 1 case as squamous cell carcinoma, 7 cases as NSCLC, and the rest 11 cases were not diagnosed at all before having a surgery.

The analysis of survival curves was based on the Kaplan-Meier method and univariate log-rank test. Overall survival (OS) was calculated from the date of having a surgery to that announcing a death. Progression free survival (PFS) was calculated from the date of having a surgery to that of identifying a progression disease or death for any cause. Significance was defined as a probability value of less than 0.05. All of the data were analyzed with the EZR software (7).

Results

The patient's characteristics are shown in *Table 1*. Briefly, the age range of the patients consisting of 17 males and 7 females was from 38 to 80 (median 70) years old. Eighteen patients were current- or ex-smokers, the size of tumor was from 15 to 125 (median 37) mm, and the pathological stage was 3 at IA, 1 at IB, 4 at IIA, 10 at IIB, 3 at IIIA and 2 at IV. Two patients had pneumonectomy, 20 lobectomy, and 2 partial resection. As the combined resected organ, 3 patients were chest wall, 5 were parietal resection and 2 were large vessel. The immunohistochemical examination showed that 7 patients were pl0, 7 were pl1, 2 were pl2, and 8 were pl3. Fourteen patients were lymphatic permeation positive, and 10 were negative. Sixteen patients were vascular invasion positive, and 8 were negative. The tissue type of epithelial components was adenocarcinoma in 12 (50%) patients, squamous cell carcinoma in 9 (37.5%), and large cell carcinoma in 3 (12.5%). The nodal status was classified as pN0 disease in 17 (71%) patients, pN1 in 4 (17%), and pN2 in 3 (13%). We investigated the epidermal growth factor receptor (EGFR) mutation by a direct sequence, and anaplastic lymphoma kinase (ALK) translocation by immunohistochemistry. We identified two cases as EGFR L858R mutation, but no case as ALK translocation. The median of Standardized Uptake Value (SUV) max and SUV average by 2-[^{18}R]-fluoro-2-deoxy-d-glucose (^{18}F-FDG) positron emission tomography (PET) was 18.29 and 10.73 for each in these 22 PC patients. ^{18}F-FDG uptake of PC patients was higher than those of usual histological types of lung cancer (8).

The 5-year OS was 54.7% (*Figure 1A*). Twenty-two patients underwent a complete resection, but two had an incomplete resection because of remaining at the parietal pleural by pathological examination in one patient and malignant pleural effusion by cytology in the other. Nine patients were recurrent. The median period until recurrence was 132 days (27 to 725 days), and recurrence within 6 months after having a resection occurred in 7 patients. The median survival time after confirming an initial relapse was 186 days (from 21 to 603 days). Eight cases were distant metastasis (2 brain, 2 bone, lung, liver, adrenal, and small intestine) and 1 case was pleural dissemination.

As a result of our analysis, we found that the correlation between OS and clinicopathological factors; vascular invasion and lymph node metastasis had a harmful effect on the OS (*Table 2*, *Figure 1B*,*C*). The 5-year PFS was 52.4% (*Figure 2A*). The analysis of the correlation between PFS and clinicopathological factors revealed that the tissue type of epithelial component, vascular invasion, and lymph node metastasis affected the PFS (*Table 2*, *Figure 2B*,*C*,*D*). On the whole, the lymph node metastasis was the factor of affecting the OS, and vascular invasion and lymph node metastasis were the factor of affecting the PFS (*Table 3*).

Discussion

Pulmonary PC is a rare histological type of lung carcinoma. Hence there is few large-scale clinical data in comparison to other common histological types of

Table 1 Clinicopathological factors (n=24)

Factor	Value	
Follow up time	Median 2.3 years (0.2–6.6 years)	
Age	Median 70 years old (38–80 years old)	
Tumor maximum size	Median 37mm (15–125 mm)	
SUV maximum (PET/CT)	Median 18.29 (7.4–34.08)	
SUV average (PET/CT)	Median 10.73 (4.57–22.71)	
Sex	Male/female	17/7
Smoking history	–/+	6/18
Tissue type of epithelial component	Adenocarcinoma/squamous/large cell	12/9/3
Operative procedure	Lobectomy/partial/pneumonectomy	20/2/2
Tumor position	RU/RM/RL/RUL/LU/LL	7/1/3/1/6/6
Chief complaint	Annual health check/bloody sputum/dyspnea/back pain/fever	15/4/1/2/1/1
Tumor marker (outlier)	CEA/CYFRA/SCC/SLX/ProGRP	5/1/3/3/1
Combined resection organ	Parietal or visceral pleura/chest wall/large vessel	5/3/2
Pleural invasion factor	0/1/2/3	7/7/2/8
T factor	1a/1b/2a/2b/3/4	1/3/5/3/11/4
N factor	0/1/2	17/4/3
Lymphatic permeation factor	–/+	10/14
Vascular invasion factor	–/+	8/16
Adjuvant therapy	Carboplatin + paclitaxel/cisplatin + vinorelbine	4/1
Neo-adjuvant therapy	Carboplatin + paclitaxel/cisplatin + vinorelbine/TS-1/UFT/radiation	4/4/4/2/1
Oncogenic driver mutation	EGFR mutation (L858R)/ALK immunohistochemistry positive	2/0

SUV, standardized uptake value; PET, positron emission tomography; CT, computed tomography; RU, right upper; RM, right middle; RL, right lower; RUL, right upper and lower; LU, left upper; LL, left lower; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

lung carcinoma. In addition, the prognostic factors and therapeutic strategy for pulmonary PC have not been found yet. The prognosis and the predictors for the long-term survival of pulmonary PC were in fact controversial. Previously pulmonary PC is considered as taking an aggressive clinical course than other NSCLCs (3-6). However, Yamamoto *et al.* (9) and Nakajima *et al.* (10) reported that the prognosis was not worse than other types of histology. In this study, we examined the correlation between the prognosis of pulmonary PC and clinicopathological factors. The 5-year OS of the 24 patients including several pathological stages was 54.7%, and the 5-year PFS was 52.4%. In comparison with other tissue types of lung cancer, the prognosis was not so poor even taking into consideration the survival curve including several progression stage (11). Nine patients faced the relapse which happened within 2-years after having a surgery. In the cases of pulmonary PC, there are two groups; one has high grade malignant property with aggressive invasion, and the other has a good prognosis if a complete resection is held.

We investigated the relation between 21 clinicopathological factors and the prognosis (OS and PFS). Since the pulmonary PC is heterogeneous, it is difficult to diagnose PC before a surgical resection. In order to predict PC before a surgery, the PET-CT in the investigated clinicopathological factors might have one possibility. The SUV max and SUV average are clearly higher than other histological types

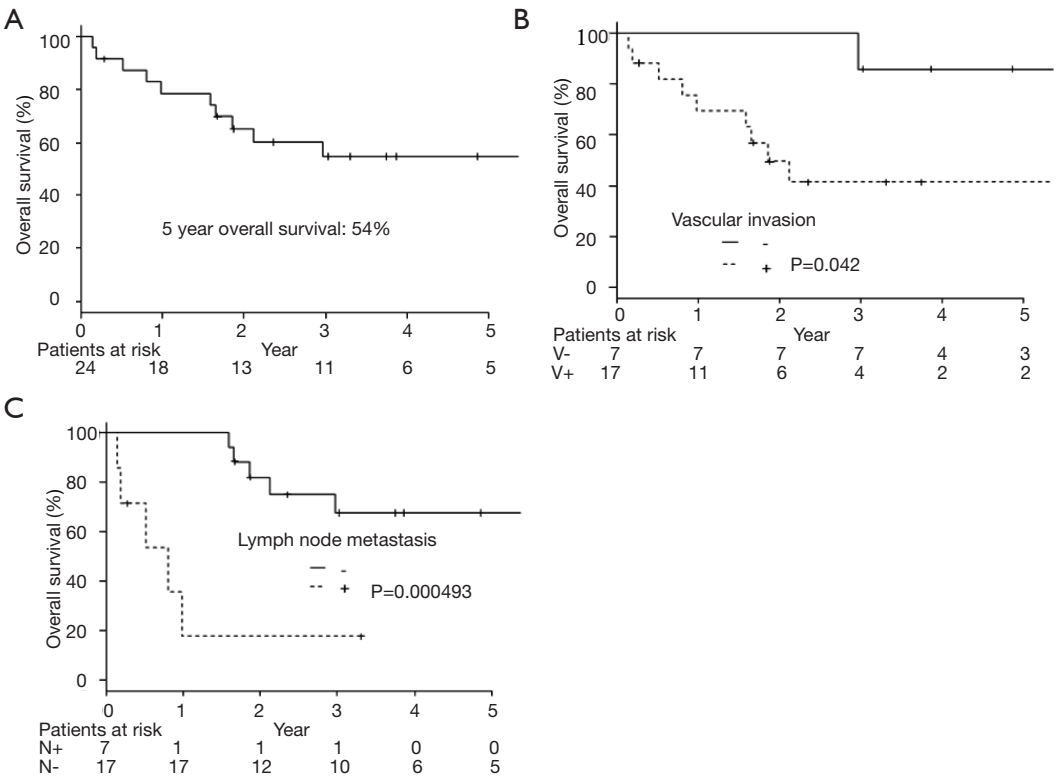

Figure 1 Overall survival curves by all patients or each clinicopathological factors. (A) Overall survival of pulmonary pleomorphic carcinoma (n=24); (B) overall survival of pulmonary pleomorphic carcinoma divided by the vascular invasion (P=0.042); (C) overall survival of pulmonary pleomorphic carcinoma divided by the lymph node metastasis (P=0.000493).

of NSCLCs (12). By taking into account the prognosis, a complete resection was the most important factor. The PC was located mainly at the peripheral lung field, invading to the parietal pleura and chest wall. However, the chest wall invasion was not a prognostic factor. In fact, the recurrence at the surgically resected edge of a chest wall was not recognized in this study. On the other hand, the lymph node metastasis and the vascular invasion were the factors deeply affected OS, and the lymph node metastasis was the only significant prognostic factor by multivariate analysis. The lymph node metastasis, the type of epithelial components, and vascular invasion affected PFS, and the lymph node metastasis and vessel invasion were significant factors by multivariate analysis. We also reviewed the recent reports of PC at *Table 4* (3,5,6,8,13-17). Just like some of the reports revealed that the lymph node metastasis was associated with a poor prognosis, our result followed those preceding reports. In this study, we didn't investigate about the sarcomatoid component as clinicopathological factor. Yuki *et al.* (5) reported the subtype of sarcomatous elements did not influence prognosis.

According to the investigation of the recurrent cases, the nine cases showed a relapse within 2years after a surgery, and most recurrent forms were distant metastases. Hence we need to find the effective chemotherapeutic drug and regimen as a neo-adjuvant and adjuvant therapy. In the one case of this study, cisplatin and vinorelbine were effective as a neo-adjuvant therapy (2 courses before surgery), and the pathological examination discovered Ef. 2b. Since the vascular invasion was associated with a poor prognosis, there is a possibility that vascular endothelial growth factor (VEGF) inhibitor would be effective for PC patients. Regarding the genetic profile of PC, some cases of EGFR activating mutation have been reported (13). Kobayashi *et al.* reported the case of transformation to sarcomatoid carcinoma in ALK-rearranged adenocarcinoma (18). Here the known genetic abnormalities associated with histological

Table 2 Correlation with overall survival plus progression free survival and clinicopathological factors (n=24)

Factor	Subgroup	Numbers	Overall survival		Progression free survival	
			5-year survival	P value	5-year survival	P value
Age	<60/≥60	7/17	57.1/54.4 (%)	0.923	57.1/40.7 (%)	0.915
Sex	Male/female	17/7	59.7/42.9 (%)	0.274	56.3/42.9 (%)	0.481
Tissue type of epithelial component	Adenocarcinoma/ others	12/12	72.7/36.5 (%)	0.0646	82.5/22.2 (%)	0.00846
Smoking history	–/+	6/18	20.8/66.2 (%)	0.104	41.7/55.0 (%)	0.686
Clinical stage	IA–IIB/IIIA	17/7	66.9/28.6 (%)	0.0655	62.7/28.6 (%)	0.121
Pathological stage	IA–IIB/IIIA–IV	18/6	61.4/33.3 (%)	0.0853	58.7/33.3 (%)	0.12
Performance status	0/1–2	13/11	57.1/51.9 (%)	0.702	67.1/36.4 (%)	0.125
Chief complaint	–/+	15/9	54.4/55.6 (%)	0.757	50.6/55.6 (%)	0.977
SUV maximum (PET/CT)	<15/≥15	7/15	57.1/49.5 (%)	0.426	71.4/44.0 (%)	0.272
SUV average (PET/CT)	<10/≥10	10/12	66.7/40.0 (%)	0.087	71.6/36.4 (%)	0.158
Tumor marker	Normal/abnormal	15/9	58.3/48.6 (%)	0.461	59.3/38.9 (%)	0.336
Chest wall resection	–/+	14/10	66.6/37.5 (%)	0.0883	62.9/40.0 (%)	0.333
Tumor position (left or right)	Right/left	12/12	57.1/55.6 (%)	0.482	58.3/46.9 (%)	0.479
Tumor position (upper/middle or lower)	Upper, middle/lower	15/9	48.2/66.7 (%)	0.745	57.8/44.4 (%)	0.455
Pleural invasion factor	0/1–3	7/17	66.7/51.0 (%)	0.416	85.7/40.3 (%)	0.111
Lymphatic permeation factor	–/+	10/14	57.1/54.5 (%)	0.475	70.0/39.7 (%)	0.126
Vascular invasion factor	–/+	7/17	85.7/41.4 (%)	0.042	87.5/32.7 (%)	0.0256
T factor	IA–IIA/IIB–IV	9/15	53.3/55.0 (%)	0.959	55.6/50.9 (%)	0.884
N factor	–/+	17/7	67.6/17.9 (%)	0.000493	64.2/19.0 (%)	0.0138
Tumor maximum size	<50/≥50	13/11	67.3/38.4 (%)	0.132	61.5/41.6 (%)	0.349
Neo-adjuvant therapy	–/+	19/5	58.2/40.0 (%)	0.216	55.8/40.0 (%)	0.489
Adjuvant therapy	–/+	12/12	50.8/58.3 (%)	0.909	46.9/58.3 (%)	0.603

SUV, standardized uptake value; PET, positron emission tomography; CT, computed tomography.

components, especially tumors with adenocarcinoma components, recommends molecular testing. We also investigated EGFR mutation and ALK translocation of the 14 cases and 24 cases each in this study. We found EGFR L858R mutation in 2 cases, and the 2 cases were treated by EGFR-TKI when we confirmed the recurrence. Erlotinib was not effective against both of these 2 patients. Including VEGF expression and the therapeutic efficacy, we should research the biological futures of PC, and develop an effective molecular targeted therapy. The research of molecular pathways will uncover the oncogenic driver mutation of pulmonary PC, and moreover give rise to an effective therapy for pulmonary PC.

In the study, we examined the relations between 21 clinicopathological factors and the prognosis in order to clarify the characteristics of pulmonary PC. The prognosis of pulmonary PC patients with lymph node metastasis, vascular invasion, and the tissue type of epithelial component worsened after their surgical resection. We have to find an effective chemotherapeutic drug or molecular targeted drug, and we should treat pulmonary PC patients by an adequate adjuvant therapy.

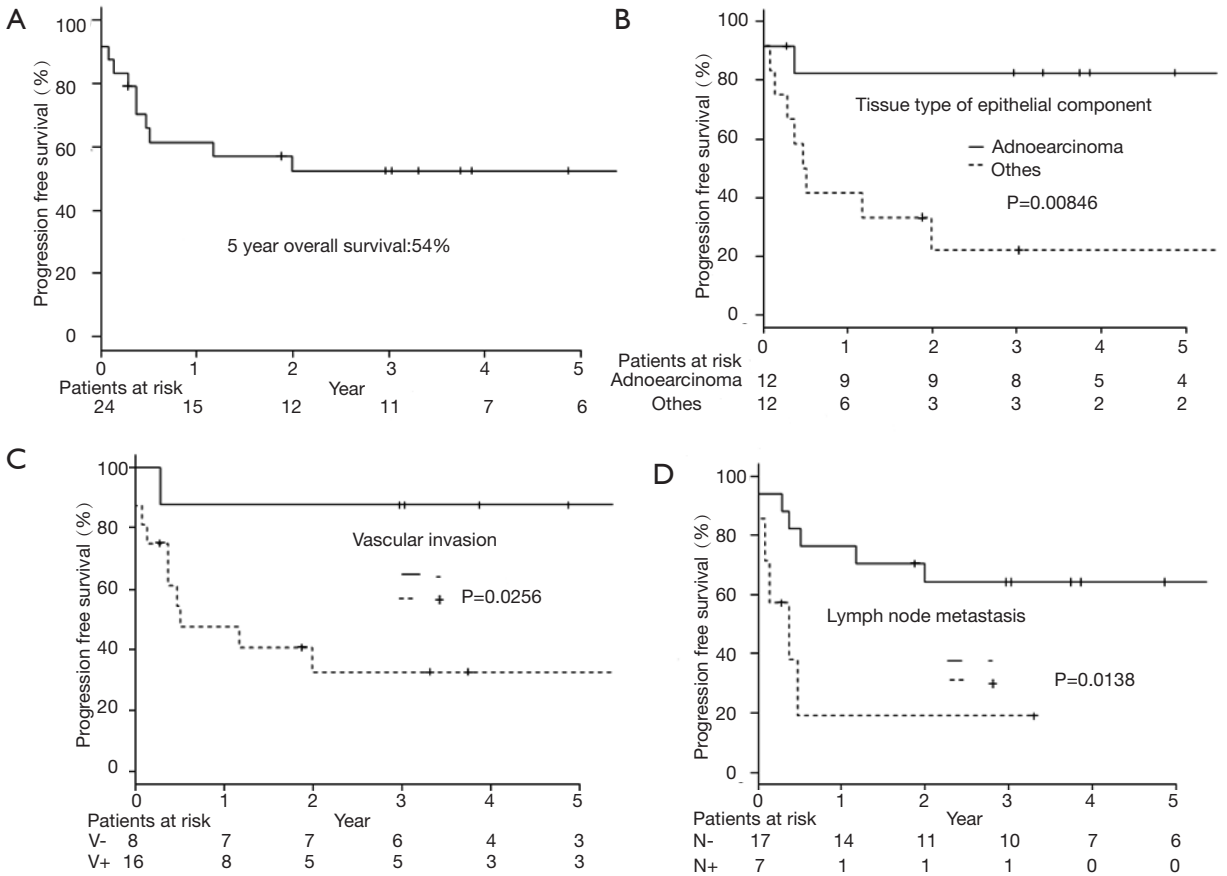

Figure 2 Progression free survival curves by all patients or each clinicopathological factors. (A) Progression free survival of pulmonary pleomorphic carcinoma (n=24); (B) progression free survival of pulmonary pleomorphic carcinoma divided by the tissue type of epithelial component (P=0.00846); (C) progression free survival of pulmonary pleomorphic carcinoma divided by the vascular invasion (P=0.0256); (D) progression free survival of pulmonary pleomorphic carcinoma divided by the lymph node metastasis (P=0.0138).

Table 3 The results of the multivariate analysis of prognostic factors influencing overall and progression free survival after surgical resection

Variable	Hazard ratio	95% CI	P value
Overall survival			
N factor	4.974	1.259 to 19.65	0.02209
V factor	3.791	0.4165 to 34.51	0.237
Progression free survival			
Tissue type of epithelial component	6.281	1.185 to 33.28	0.03080
V factor	2.271	0.2426 to 21.26	0.4723
N factor	4.608	1.1010 to 19.29	0.03649

Table 4 The reports of the surgically resected pulmonary pleomorphic carcinoma

Reports	Patients number	Prognostic factors (overall survival)	Progression free survival factors	Others
Fishback (1994)	78	Pathological stage, tumor size, lymph node metastasis	-	Type of epithelial components was no prognostic factor
Yuki (2007)	45	Lymph node metastasis	lymph node metastasis	-
Yamamoto (2007)	21	None	lymph node metastasis	-
Mochizuki (2008)	70	Pathological stage, lymph node metastasis, necrosis	-	type of epithelial components was no prognostic factor
Ito (2010)	22	Surgical resection	-	resistant to chemotherapy (gefitinib was partial response for 1 patient)
Kaira (2010)	17	Surgical resection	-	3/17 patients were EGFR mutation positive
Tsubata (2012)	75	VEGF expression	-	-
Chen (2012)	26	Pleural invasion, pathological edge	None	-
Miyahara (2015)	62	Positive for ZEB1 expression	-	-
Okuda (this report)	24	Lymph node metastasis, vascular invasion	lymph node metastasis, type of epithelial components, vascular invasion	Neo-adjuvant therapy CBDCA+PTX for 4 patients/SD, Ef1a about all CDDP+VNR for 1 patient/ PR, Ef2a

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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