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Clinical characteristics and prognosis of nonsurgically treated patients with pneumonic-type adenocarcinoma

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Abstract

Pneumonic-type adenocarcinoma (P-ADC) is a subtype of lung adenocarcinoma with high mortality, which often requires lobectomy surgery. Nonsurgically treated P-ADC patients usually have more advanced or complex conditions, which remain poorly understood and pose a major challenge in clinical management. We aimed to describe the clinical profiles and prognosis of non-surgically treated P-ADC patients. We enrolled 71 patients with pathologically proven P-ADC from a university hospital in China. Clinical and laboratory data were retrieved from medical record. Their median age was 62 years, including 45% men and 35% smokers. Clinical manifestations were dominated by cough, sputum, and dyspnea. Main chest imaging features included nodules, shadow, consolidation, and air bronchogram. Nearly half or more of patients showed higher levels of inflammation and cancer biomarkers including cytokeratin-19-fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA). Majority of patients were classified at the stage IIIB or IV. Palliative care was the most popular treatment option but provided a shorter overall survival compared to tyrosine kinase inhibitor therapy, standard chemotherapy, and sequential therapy while there were no significant differences in the survival among the latter 3 options. Higher serum CEA was associated with longer survival and better prognosis while higher serum CYFRA 21-1 could predict a poor prognosis. Detailed understanding the clinical characteristics and prognostic factors in nonsurgically treated P-ADC may allow the identification of patients with particular risk factors and initiation of early and specific treatment in order to optimize outcomes.

Abbreviations: ALK = anaplastic lymphoma kinase, BAC = bronchoalveolar carcinoma, BAL = bronchoalveolar lavage fluid, CEA = carcinoembryonic antigen, CI = confidence interval, CT = computed tomography, CYFRA21-1= cytokeratin-19-fragment, EBUS-GS-TBLB = endobronchial ultrasound transbronchial lung biopsy with guide-sheath, EGFR = epidermal growth factor receptor, HR = hazard ratio, NCCN = National Comprehensive Cancer Network, NSE = neuron-specific enolase, P-ADC = pneumonic-type adenocarcinoma, PET/CT = positron emission tomography, ProGRP = progastrin-releasing peptide, PTLB = percutaneous needle aspiration biopsy of the lung, SCC = squamous cell carcinoma antigen.

Keywords: carcinoembryonic antigen, clinical characteristics, pneumonic-type adenocarcinoma, prognostic factor, survival time, treatment

1. Introduction

Tracheal, bronchus, and lung cancer are the leading causes of cancer deaths worldwide,[1] of which adenocarcinoma is the most common histological type.[2] Pneumonic-type adenocarcinoma (P-ADC), a subtype of adenocarcinoma, has been a controversial subject over the past century[3–7] following its initial recognition in 1903 as a diffuse infiltrative type of lung cancer that simulates pneumonia.[8] Symptoms of P-ADC are nonspecific. Typical chest radiographic findings (mostly by computed tomography [CT]) include an air-filled bronchus within the consolidation with stretching, squeezing, sweeping, widening of the branching angle, and bulging of the interlobar fissure.[9,10]

Due to nonspecific manifestations, P-ADC can be easily misdiagnosed as pneumonia, tuberculosis, or other diseases, such as interstitial lung disease or pulmonary vascular disease, especially in developing countries where many patients in the early stage refuse invasive examinations.[11,12] The most effective treatment option for P-ADC is surgical resection though the 5-year survival rate of surgically treated P-ADC patients is approximately 30% to 68%.[7,13,14] Patients with nonsurgical treatment account for 14% to 60% of P-ADC patients,[7,15] but their clinical characteristics and prognosis are not well understood.

The primary goal of this study was to investigate the clinical characteristics, laboratory profiles, treatment outcomes and prognosis of P-ADC in a cohort of 71 patients undertaking nonsurgical treatment in a university hospital in Southwestern China.

Editor: Kou Yi.

JW and DT contributed equally to this study.

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:18(e15420)

Received: 7 October 2018 / Received in final form: 20 January 2019 / Accepted: 4 April 2019

http://dx.doi.org/10.1097/MD.0000000000015420

Table 1

Demographic and clinical characteristics of 71 enrolled patients with pneumonic-type adenocarcinoma.

Categories	No. of patients	%
Age, yr		
Mean	60.6	
Range	25–91	
Adult (18–59 yr)	32	45.1
Elderly (≥60 yr)	39	54.9
Gender (male)	32	45.1
Former/current smoker	25	35.2
Former/current alcohol drinker	16	22.5
Stage (IIIB or IV)	64	90.1
Overall survival, mo		
Median	7.5	
Range	1–42	
Pulmonary or systemic symptoms and signs		
Cough	62	87.3
Chronic cough (≥8 wk)	30	42.3
Subacute cough (3–8 wk)	23	32.4
Acute cough (≤3 wk)	9	12.7
Sputum	48	67.6
White frothy sputum	27	38.0
White sticky sputum	9	12.7
Purulent sputum	12	16.9
Dyspnea	37	52.1
Chest pain	25	35.2
Hemoptysis	11	15.5
Fever	5	7.0
Rale	22	31.0
Moist rale	15	21.1
Rhonchi	7	14.1

Table 2

Radiological features and laboratory test results of 71 enrolled patients.

Categories	No. (%) of patients
Radiological features	
Bilateral lesion	38 (53.5)
Unilateral lesion	33 (46.5)
Multiple lobe involvement	54 (76.1)
Single lobe involvement	17 (23.9)
Nodular	40 (56.3)
Patchy shadow or shaggy cloudy shadow	28 (39.4)
Consolidation	11 (15.5)
Air-bronchogram	9 (12.6)
Cavity	5 (7.0)
Mucous bronchogram	2 (2.8)
Pleural effusion	45 (63.3)
Pericardial effusion	11 (15.5)
Laboratory parameters	N increased/ N assessable (%)
WBC (normal: 3.5–9.5 × 10^9/ l)	17/69 (24.6)
Neutrophil (normal: 50%–70%)	38/69 (55.1)
CRP (normal: <10 mg/l)	29/51 (58.0)
ESR (M:2–21, F: 2–25 mm/h)	17/28 (60.7)
PCT (normal: <0.05 μg/l)	32/51 (72.7)
CEA (normal: 0.2–10 ng/ml)	28/64 (43.8)
NSE (normal: 0.05–13 ng/ml)	28/56 (50.0)
CYFRA21–1 (normal:0.1–3 ng/ml)	53/62 (85.5)
SCC (normal: 0–1.5 ng/ml)	6/55 (10.9)
ProGRP (normal:25–77 ng/ml)	9/38 (23.7)
Pleural effusion CEA (normal: 0.2–10 ng/ml)	17/20 (85.0)
EGFR mutation	10/25 (41.7)

CEA = carcinoembryonic antigen, CRP = C reactive protein, CYFRA21-1 = cytokeratin-19-fragment, EGFR = epidermal growth factor receptor, ESR = erythrocyte sedimentation rate, F = female, M = male, NSE = neuron-specific enolase, PCT = procalcitonin, ProGRP = progastrin-releasing peptide, SCC = squamous cell carcinoma antigen, WBC = white blood cell.

2. Methods

The study was approved by the Institutional Review Boards of the First Affiliated Hospital of Chongqing Medical University in China and written informed consent was obtained from all subjects. Data was collected through electronic medical record system and interview of patients and/or their kin.

2.1. Patients, inclusion criteria, and data collection

We performed a medical review of all patients with pathologically-proven adenocarcinoma from June 2013 to August 2016 in the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Pathological diagnosis included cytological and histological analyses. Cytological analysis was performed on exfoliated cells in sputum, bronchoalveolar lavage fluid (BAL) and pleural effusion. Histological exams were carried out on CT-guided percutaneous needle aspiration biopsy of the lung (PTLB), endobronchial ultrasound trans-bronchial lung biopsy with guide-sheath (EBUS-GS-TBLB) or superficial lymph node needle biopsy. For each patient, we retrieved the reports of cytological and pathological tests along with all clinical information, including demographic data, symptoms, and signs (Table 1), radiological and other laboratory reports (Table 2), and treatment regimens and outcomes. Radiological tests included chest X-ray, CT and positron emission tomography (PET-CT). Other laboratory tests included white blood cell and neutrophil counts, C reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), procalcitonin (PCT), serum, and pleural fluid biomarkers for cancer including epidermal growth factor receptor (EGRF) mutations and *anaplastic lymphoma kinase* (*ALK*) gene rearrangement. All blood samples were collected from patients after fasting overnight before treatment.

Patient inclusion criteria included all of the following:

Diagnosis of lung adenocarcinoma confirmed by histological and/or cytological test;

Radiological presentation of pneumonic infiltrate or consolidation with ground-glass opacities and air-filled bronchi but without significant presence of discrete nodules;

No evidence of concurrent pulmonary infections or obstructive pneumonia;

Received treatment with EGFR tyrosine kinase inhibitors (TKI), chemotherapy, palliative care, or combination of these treatments (Table 3) but without surgical resection.

Exclusion criteria of the study protocol included an operative history of any cancers and pancreatitis.

All patients were enrolled in September 2016 and followed until April 2017 (endpoint). The stage of lung cancer (TNM stage) at enrollment in each patient was assessed according to the seventh edition of International Union Against Cancer (UICC) for Lung Cancer staging guideline.[16] Overall survival time was calculated from the date of diagnosis to the date of death.

2.2. Statistical analysis

Categorical variables were summarized as frequencies and analyzed by Chi-square test or Fisher exact test. Continuous

Table 3

Comparison of 4 groups with different treatment regimens.

Baseline demographics	Chemotherapy* (n=20)	TKI therapy* (n=8)	Palliative care* (n=37)	Sequential therapy* (n=6)	*P*-value
Gender (male)	11 (55.0)	2 (25.0)	16 (43.3)	3 (50.0)	.619
Mean age, yr	62 (25, 81)	59 (42, 89)	66 (33, 91)	52 (41, 61)	.072
Smoking	9 (45.0)	1 (12.5)	13 (35.1)	3 (50.0)	.878
Alcohol drinking	5 (25.0)	2 (25.0)	6 (16.2)	0 (0)	.183
Bilateral lesion	10 (50.0)	1 (12.5)	21 (56.8)	4 (66.7)	.873
Multilobe lesion	16 (80.0)	7 (87.5)	33 (90.2)	5 (83.3)	.820
Pleural effusion	13 (65.0)	2 (25.0)	26 (70.3)	3 (50.0)	.800
High serum CEA	5 (33.3)	5 (62.5)	14 (41.2)	4 (66.7)	.367
High serum ProGRP	1 (14.3)	1 (25.0)	7 33.3)	0 (0.0)	.349
High serum SCC	2 (18.2)	0 (0.0)	3 (10.0)	1 (16.7)	.613
High serum CYFRA21–1	10 (66.7)	8 (100.0)	30 (90.9)	5 (83.3)	.092
High serum NSE	3 (27.3)	5 (62.5)	18 (60.0)	2 (33.3)	.202
Stage (III B or IV)	17 (85.0)	7 (87.5)	34 (91.9)	6 (100.0)	.696
Overall survival time, mo	9 (1, 42)	12 (9, 15)†	3 (1, 20)	15 (4, 24)‡	.026

CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin-19-fragment, NSE = neuron-specific enolase, ProGRP = progastrin-releasing peptide, SCC = squamous cell carcinoma antigen.

* Values are shown as median (range) for age or no. (%) for other variables.

† Compared with palliative care, $P = .034$.

‡ Compared with palliative care, $P = .016$.

variables were summarized as means with standard deviation and analyzed by ANOVA and *t* test. Correlation of survival rates with demographic and clinical factors was assessed by the Kaplan–Meier method. Survival curves were compared using the log-rank test with a threshold of significance set at a 2 side $P < .05$. Cox multiple regression method was used for multivariate analysis. Significant variables (with $P < .2$) in log-rank tests and main clinical factors potentially affecting survival time were further assessed by Cox multivariate regression analysis. All statistical analyses were conducted using the SPSS version 22 (IBM SPSS for Windows, Version 22.0, IBM Corp. Armonk, NY).

3. Results

We enrolled a total of 71 patients with P-ADC meeting the inclusion criteria. Of these 71 patients, 60 were confirmed by cytological analysis of BAL (22 patients), sputum (6 patients), or pleural effusion specimens (32 patients), 10 were confirmed by histological exams of biopsy specimens obtained through PTLB or EBUS-GS-TBLB (9 patients) or superficial lymph node needle (1 patient), and 1 was confirmed by cytological analysis of pleural effusion, BAL, and sputum specimens. Pleural biopsy, open lung biopsy, or mediastinoscopy was never performed in any patients enrolled.

The enrolled patients included 32 men (45.1%) and 39 women (54.9%); their median age was 62 years (range: 25–91 years), with 52 (73.2%) patients older than 55 years and 19 (16.8%) patients less than 55 years old (Table 1). Twenty-five (35.2%) patients were current or former smokers. Sixty-two patients were accompanied with noncancer diseases, including hypertension (13 patients, 18.3%), connective tissue disease (5% or 7%), hepatitis B (4% or 5.6%), diabetes mellitus (4% or 5.6%), COPD (3% or 4.2%), coronary heart disease (2% or 2.8%), and venous thrombosis (2% or 2.8%). One patient had a history of breast cancer, which was treated by surgical resection followed by adjuvant chemotherapy more than 5 years ago. Another patient was diagnosed hypophysoma 8 years ago and remained stable through the observed period in this study. Follow-up was 100% for a median of 6 months (range 1–42 months).

3.1. Clinical manifestations

Sixty-two (87.3%) patients experienced cough, including 30 (42.3%) patients with chronic cough (lasting >8 weeks), 23 (37%) with subacute cough (lasting 3–8 weeks), 9 (14.6%) with acute cough (<3 weeks). Forty-eight (67.6%) patients experienced sputum, including 27 with white frothy sputum, 9 with white sticky sputum, and 12 with purulent sputum. Eleven (15.5%) patients experienced both sputum and hemoptysis. Other main manifestations included chest pain in 25 (35.2%) patients, dyspnea in 37 (52.1%) patients, moist rale or rhonchi in 22 (30%) patients, and fever in 5 (7%) patients (Table 1).

3.2. Radiological features and laboratory findings

Only 2 of the 71 enrolled patients received chest X-ray exam while all the others received chest CT or PET-CT. Multilobe involvement was more common than single-lobe involvement (76% vs 24%). The prevalence of unilateral lesions was very close to that of bilateral lesions (46.5% vs 53.5%). Morphological appearances of CT scan included pleural effusion (n=45, 63%), nodules (n=40, 56%), patchy shadow or shaggy cloudy shadow (n=28, 39%), consolidation (n=11, 16%), pericardial effusion (n=11, 16%), and air bronchogram (n=9, 13%). Air and mucous bronchograms were rare (each <10%; Table 2)

Blood cell count showed higher white blood cell or neutrophil count in 25% and 55% of patients, respectively. More than half of patients had elevated levels of inflammation biomarkers including CRP (58%), PCT (73%), and ESR (61%). Higher levels of serum cancer biomarkers were noted in 86% of patients for cytokeratin-19-fragment (CYFRA21-1), 44% for carcinoembryonic antigen (CEA), 50% for neuron-specific enolase (NSE), 24% for progastrin-releasing peptide (ProGRP), and 11% for squamous cell carcinoma antigen (SCC) (Table 2). The mean concentration of serum CEA was 76.4 ng/ml and that of CYFRA21-1 was 13.7 ng/ml. The total number patients tested for blood cell counts, CRP, ESR, PCT, CEA, NSE, CYFRA21-1, SCC, ProGRP, pleural effusion CEA are 69, 51, 28, 51, 64, 56, 62, 55, 38, and 20, respectively.

EGRF mutations were present in 10 (41.7%) out of 25 patients tested, including 1 with G719X mutation in exon 18, 5 with a multibase deletion mutation in exon 19, 4 with L858K mutation in exon 21. *ALK* rearrangement was detected in only 1 of 5 patients tested. All of these mutations and rearrangement have been reported previously to be associated with P-ADC.[17]

3.3. TNM stage classification, treatment, and survival times

Of the 71 enrolled patients, 64 (90.1%) were firstly diagnosed at a rather late stage (IIIB or IV stage), 5 (7%) at stage IIIA and 2 (2.9%) at stage IA.

Four different main treatment options were applied (Table 3), including:

Eight patients with EGFR mutations received TKI therapy with icotinib, erlotinib, or gefitinib; their median survival time was 12 months (range: 9–15 months).

Twenty patients received platinum-based chemotherapy regimens including pemetrexed, paclitaxel, and docetaxel administered to 8, 10, and 8 patients, respectively. The median survival time of these 20 patients was 9 months (range: 1–42 months).

Six patients were first treated with 1 to 4 courses of chemotherapy and then switched to TKI therapy (referred to as sequential therapy); all of them showed poor responses, with a median survival time of 15 months (range: 4–24 months).

Thirty-seven patients received palliative care, with a median survival time was 3 months (range: 1–20 months).

Comparison among the 4 groups of patients with different treatments showed no significant differences in any demographic factors, clinical manifestations, laboratory findings, or TNM stages (Table 3). However, there was a significant difference in the overall survival (OS) time among these 4 groups ($P=.026$). Compared with patients receiving palliative care, patients receiving TKI therapy or sequential therapy had longer OS ($P=.034$ or .016, respectively). There were no differences in OS in pair-wise comparison among patients with chemotherapy, TKI therapy, and sequential therapy.

3.4. Survival and prognostic factors

At the endpoint of this study, 60 patients died while 11 patients survived. The median survival time of all these 71 patients was 7.5 months (range: 1–42 months). Log-rank test indicated that different treatment regimens might affect the survival time ($P=.014$). Based on the distribution statistics, the variances of the 4 treatment groups were homogeneous (Table 3). When analyzed using Kaplan–Meier method, a statistical significance ($P=.018$) was observed in the difference in age among the 4 groups. Cox multivariate regression was employed to build a model with hazard ratio (HR) for the following variances: gender, age, smoking status, alcohol drinking history, radiological features, cancer biomarkers, and treatment methods (Table 4). Palliative care yielded a worse OS compared to TKI therapy (HR = 5.64, 95% CI 1.093–29.168, $P=.039$), chemotherapy (HR = 3.321, 95% CI 1.045–10.552, $P=.042$), and sequential therapy (HR = 16.015, 95% CI 1.172–218.837, $P=.038$). Higher serum CEA level predicted a good prognosis (HR = 0.278, 95% CI 0.082–0.920, $P=.039$) while an elevated serum CYFRA 21-1 level predicted a worse prognosis (HR = 12.786, 95% CI 2.207–74.066, $P=.004$) (Fig. 1). Other factors did not appear to be independent predictor for the prognosis of P-ADC.

Table 4

Hazard ratio (HR) for overall survival by Cox multiple regression analysis of 71 patients with pneumonic-type adenocarcinoma.

	HR (95%CI)	*P*-value*
Age	0.965 (0.277–3.360)	.955
Gender (male)	3.990 (0.811–19.628)	.089
Alcohol drinking	0.348 (0.090–1.344)	.126
Smoking	4.774 (0.887–25.692)	.069
Treatment		.018
Palliative care versus TKI	5.647 (1.093–29.168	.039
Palliative care versus Chemotherapy	3.321 (1.045–10.552)	.042
Palliative care versus sequential therapy	16.015 (1.172–218.837)	.038
Multilobe lesion	0.429 (0.133–1.389)	.158
Bilateral lesion	1.298 (0.460–3.667)	.622
Pleural effusion	0.968 (0.420–2.229)	.939
High serum CYFRA211	12.786 (2.207–74.066)	.004
High serum ProGRP	1.515 (0.827–2.777)	.179
High serum CEA	0.278 (0.082–0.920)	.039
High serum NSE	0.587 (0.268–1.286)	.190

CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin-19-fragment, ProGRP = progastrin-releasing peptide.
* Under-lined are values with statistical significance.

We further compared variances between patients with normal CEA levels and those with higher CEA levels (Table 5), and found that only OS was significantly different (4 months vs 11 months, $P=.029$) while all other variances were homogeneous.

4. Discussion

Although being in a smaller population than surgically treated patients, nonsurgically treated patients with P-ADC usually have more advanced or complex conditions, thus posing a great challenge in clinical management. To better understand the clinical characteristics and prognosis of this patient population, we initiated this retrospective study in a teaching hospital in Chongqing, China involving 71 patients with cytologically and/or histologically proven P-ADC undertaking nonsurgical treatment.

We first evaluated demographic factors of the enrolled patients (Table 1). Their ages ranged from 25 to 91 years old, similar to the range of 15 to 87 years old in previous studies.[5–7,18–20] The ratio of male and female patients in this study was almost equal (45% of males), which was in contrast to previous reports with either a male-dominated (57%–70%) or female-dominated (63%–71%) trend.[5–7,18,20] Smokers accounted for about one-third of our patient population though smoking was found to be irrelevant to the survival time of P-ADC, consistent with previous studies.[21,22]

Next, we evaluated clinical manifestations of the enrolled patients. Majority (75%) of them presented cough more than 3 weeks without fever, which is obviously in contrast to acute pneumonia (Table 1). Our observation of cough as the most common symptom was similar to the report of Wislez et al.[7] This suggests that in patients presenting a pneumonia-like image with non-acute cough but without fever, clinicians should be alert to considering the possibility of P-ADC and necessity of specific diagnostic tests. The observation of high prevalence of asymptomatic patients in several previous studies could be explained by the dominance of stage I lung cancer.[4–6,19] We observed higher frequencies of dyspnea (52%) and hemoptysis (16%) compared to the reports of Liu et al (2.2% for dyspnea)[23]

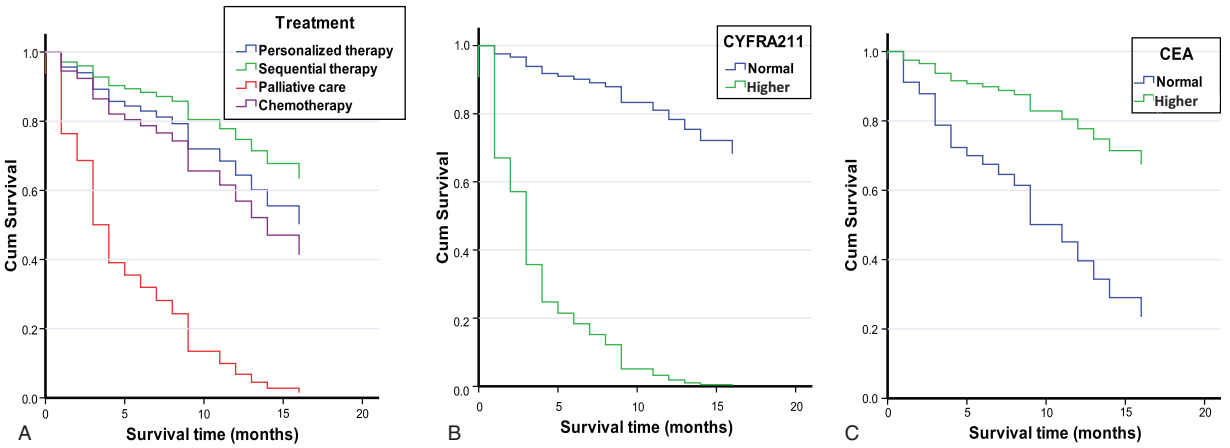

Figure 1. Overall survival curves by quartile of treatment options, CYFRA21-1 and CEA in Cox multiple regression analysis. (A) Patients receiving palliative care had a trend towards shorter overall survival compared to other 3 quartile ($P = .018$). (B) Patients with higher CYFRA21-1 had a trend towards shorter overall survival compared to patients with normal CYFRA21-1 levels ($P = .004$). (C) Patients with higher CEA had a trend towards improved overall survival compared to patients with normal CEA levels ($P = .039$). CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin-19-fragment.

and Regnard et al (8.6% for hemoptysis).[6] This difference could be explained by the fact that majority (90%) of our patients were at a rather late stage of P-ADC (IIIB or IV stage), with high frequencies of multilobe involvement (76%) and pleural metastasis (63%) (Table 2). Five of our patients had fever, which has never been reported before in the literature. The cause of fever was not identified though none of them had evidence of infection in the respiratory and other systems.

Chest imaging revealed an almost equal bilateral and unilateral involvement (54% vs 47%), with the lesions presenting mostly as nodules (56%) and less frequently as shadow (39%) and consolidation (16%) (Table 2), which could be easily confused with pneumonia. The frequency of bilateral lesions and nodules in our patients appeared to be similar to that reported by Jung et al[9] and Ebright et al[24] but higher than that of Daly et al[14] and lower than that of Lyons et al[25] The higher frequency of nodules in Lyons et al[25] might be due to the larger proportion of patients (>50%) at an early stage of illness (IA). Although consolidation has been reported to be very common,[9,10] it was detected in only 16% of our patients. The frequency of pleural effusion is similar to that reported previously.[7,9] Air-bronchogram was detected in only 13% of our patients though it has been reported to be a main distinct radiological feature for P-ADC in some studies.[6,9] All the above-mentioned radiographic presentations are not specific for P-ADC; thus other diagnostic tests are required to confirm the diagnosis of P-ADC and differentiate it from other pulmonary diseases.

We also assessed the profiles of molecular biomarkers in P-ADC patients (Table 2). More than half (58.8%) of our patients showed higher levels of inflammation biomarkers including CRP and PCT. In addition, many patients showed elevated levels of cancer biomarkers, including serum CYFRA21-1 in 87% of patients, serum NSE in 50% of patients, serum CEA in 44% of patients, and pleural CEA in 85% of patients. The elevation of these biomarkers, which has not reported previously in P-ADC patients, suggests their potential usefulness for diagnosis and prognostic prediction of P-ADC as discussed below. While EGFR mutations have been shown to be present in 50% to 75% of patients with P-ADC,[26,27] and recommended, along with *ALK* rearrangement and other genetic alterations, for adenocarcinoma screening by the international panel and National Comprehensive Cancer Network (NCCN),[26] only 41% of our patients had EGFR mutations, consistent with a previous report from the same region in China.[28]

Table 5

Comparison of pneumonic-type adenocarcinoma patients with normal or elevated serum carcinoembryonic antigen.

Baseline factors	Normal CEA (n = 36)	High CEA (n = 28)	*P*-value*
Age, yr	65 (29, 89)	58 (38, 91)	.110
Gender, male/female	19/36 (52.8)	10/28 (35.7)	.211
Smoker	16/36 (44.4)	7/28 (25.0)	.124
Alcohol drinker	8/36 (22.2)	4/28 (14.3)	.527
Underlying or accompanying diseases	15/36 (41.7)	11/28 (42.9)	>.99
Stage of IIIB or IV	33/36 (91.7)	28/28 (100.0)	.251
Palliative care	21/36 (58.3)	14/28 (50.0)	.615
EGFR mutations	3/11 (27.8)	8/11 (72.7)	.086
High serum CYFRA21–1	28/36 (77.8)	26/27 (96.3)	.066
Pleural effusion	18/36 (50.0)	20/28 (69.0)	.128
Overall survival, mo	4 (1, 42)	11 (1, 42)	.029

CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin-19-fragment, EGFR = epidermal growth factor receptor.
* Values are shown as median (range) or no. (%).

When comparing the treatment options for nonsurgically treated P-ADC patients, we found that palliative care was the most popular option (52% of patients) but provided the shortest survival time (3 months; Table 3). This mirrors the older age, higher prevalence of multilobe involvement and pleural effusion, higher co-morbidity, and later TNM stage of the patient group receiving palliative care. Sequential therapy and TKI therapy appeared to yield longer survival times than palliative care and therapy in this study, which supports previous findings[29–31] and the current recommendation of NCCN to use the former 2 options as the first line therapy for adenocarcinoma patients.[26] However, there were no statistically significant differences in the survival time among patients with chemotherapy, TKI therapy, and sequential therapy. Clearly, these observations await further investigation using a larger sample size and a case-control design.

One of the most striking findings in this study is the association of higher serum CEA level with longer survival and better prognosis in P-ADC patients (Tables 4 and 5 and Fig. 1), which has not been reported previously. This observation is consistent with the study of Veronesi at al,[32] who found tumor CEA as an independent predictor of better outcome in squamous cell carcinoma of the lung though CEA has been reported to be a risk factor for adenocarcinoma in some studies.[33,34] Further studies are needed to elucidate the value of CEA as a prognostic factor. In this study, we also found elevated serum CYFRA 21-1 to be associated with a poor prognosis as has been reported previously.[35,36] But we did not found an association between radiological features and the survival of P-ADC patients as reported previously.[3]

The main limitations of this study included the small number of participants from a single hospital, the short follow up duration, and the lack of a control group. Certainly, further studies are needed of a case-control design including a larger number of patients in a multicenter setting.

5. Conclusions

In this cohort study, we assessed the clinical characteristics, laboratory findings, and treatment options and outcomes of 71 non-surgically treated patients with P-ADC from a single hospital. The main novelties of this study include:

The first report focusing on nonsurgically treated patients with P-ADC;

Demonstration for the first time of the association of higher serum CEA level with longer survival and better prognosis in P-ADC patients.

Detailed understanding of the clinical characteristics and prognostic factors in nonsurgically treated P-ADC may allow the identification of patients with particular risk factors and initiation of early and specific treatment in order to optimize outcomes.

Acknowledgments

We wish to thank Dr Liang Ma at the National Institutes of Health, Bethesda, Maryland for critical review of the manuscript.

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