



Pulmonary enteric adenocarcinoma

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ABSTRACT

Pulmonary enteric adenocarcinoma (PEAC) is an exceptionally rare subtype of non-small cell lung cancer (NSCLC). It is characterized by pathological features similar to those of colorectal adenocarcinoma. Most patients with PEAC have almost no special clinical manifestations, and it is often difficult to differentiate from metastatic colorectal adenocarcinoma (MCRC). As a special type of lung adenocarcinoma, PEAC has unique mutation expression and immune characteristics; its mutation profile shows higher Kirsten rat sarcoma viral oncogene (*KRAS*), human epidermal growth factor receptor-2 (*HER2*), DNA mismatch repair (*MMR*) mutation rates, and much lower epidermal growth factor receptor (*EGFR*) rate. So in the future, targeted therapy may tend to be a new light in the treatment of PEAC. As for immunohistochemistry (IHC), CDX-2, villin, and CK7 are significantly positive in PEAC. This review focuses on the pathologic features, immunohistochemical examination, mutation analysis, diagnosis, treatment, and prognosis of PEAC.

Introduction

Pulmonary enteric adenocarcinoma (PEAC) is an exceptionally rare subtype of non-small cell lung cancer (NSCLC), which was first described by Tsao and Fraser in 1991 [1]. Up to now, only nearly 216 cases have been reported [3-14]. In 2011, PEAC was officially declared as a separate variant of invasive lung adenocarcinoma in the international multidisciplinary classification of lung adenocarcinoma and was subsequently proposed by the World Health Organization (WHO) classification in 2015 [15,16]. PEAC is defined as a type of primary pulmonary adenocarcinoma, which contains more than 50% enteric differentiation component, and the cancer cells must be positive for one or more immunohistochemical markers of gastrointestinal tumors [16]. As a distinct subtype of lung adenocarcinoma, PEAC has atypical morphological and immunohistochemical features with a high resemblance to metastatic colorectal adenocarcinoma (MCRC). The epidemiological characteristics and clinical manifestations of PEAC are indistinct; therefore, the correct diagnosis of PEAC needs a combination of clinical manifestations, laboratory tests, histopathology, immunohistochemistry, and mutational analysis. However, the treatment of PEAC has not been fully studied in previous literatures. The present treatment strategy is the same as that of primary lung adenocarcinoma; that is, according to the different clinical

stages, a comprehensive treatment is chosen, which is primarily surgical treatment—supplemented by chemotherapy, radiotherapy, and/or targeted therapy. With the development of molecular pathology, PEAC has been explored in depth in recent years, but primary focus is on clinical pathology, immunohistochemistry, and mutational analysis. Further studies and clinical trials should focus on the exploration of the treatment and prognosis of PEAC.

Epidemiological characteristics

Epidemiologically, PEAC is a relatively rare variant of lung adenocarcinoma. Detailed results of epidemiological characterization are summarized in Table 1. In general, the overall prevalence of PEAC in NSCLC and primary pulmonary adenocarcinoma is 0.5% and 0.68%, respectively [3]. A large proportion of the patients are elderly (so far, the reported age of the youngest patient is 34 years [5]), the mean age of the patients is 50–60 years. In terms of the sex ratio, 17 patients with PEAC were analyzed in the study of Lin et al., and it was concluded that both sexes have a similar incidence of PEAC [7,9,17-20]. The gender-specific morbidity remains controversial because of the limitation of small case numbers in existing reports.

Recent epidemiological studies have confirmed that lung adenocarcinoma typically occurs in nonsmoking women or those who have quit

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Table 1
The reported clinical characteristics and outcomes of PEAC.

| Ref. | No. of cases | Age | | Sex | | Positive serum tumor markers | | | | Stage | | Follow-up (M) | | Alive | Not available | | |
|------|--------------|----------------|--------|------|--------|------------------------------|-------|-------|------------|-------|-----|---------------|--------------|-----------|---------------|---------------|------|
| | | Median (range) | Age>60 | Male | Female | Smoking | CEA | CA199 | CYFRA 21-1 | CA125 | NSE | Stage I/II | Stage III/IV | | | Median(range) | Died |
| [4] | 18 | 63.2(55-76) | 11 | 6 | 12 | 4 | 6 | 9 | 2 | NM | 0 | 12 | 6 | 31(4-96) | 3 | 13 | 2 |
| [5] | 28 | 64.8(43-82) | 21 | 22 | 6 | 8 | NM | NM | NM | NM | NM | 19 | 9 | 24(13-31) | 6 | 19 | 3 |
| [6] | 23 | 59.5(41-76) | NM | 15 | 8 | NM | 10/14 | 5/10 | NM | 5/10 | NM | NM | NM | NM | NM | NM | NM |
| [7] | 9 | 65(34-74) | 7 | 4 | 5 | 6 | NM | NM | NM | NM | NM | 7 | 2 | 25(6-43) | 3 | 6 | 0 |
| [8] | 30 | NM | 17 | 9 | 21 | NM | 28/30 | NM | NM | NM | NM | 27 | 3 | NM | NM | NM | NM |
| [9] | 7 | NM | NM | 6 | 1 | 7 | NM | NM | NM | NM | NM | 5 | 2 | 30(12-43) | 2 | 5 | 0 |
| [10] | 1 | 62 | 1 | 1 | 0 | 1 | 1 | 0 | NM | NM | NM | 1 | 0 | NM | NM | NM | NM |
| [11] | 6 | 71.5(57-82) | 5 | 1 | 5 | NM | NM | NM | NM | NM | NM | 6 | 0 | 3(2-7) | 3 | 3 | 0 |
| [12] | 46 | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM |
| [13] | 7 | 64.1(43-77) | 5 | 4 | 3 | 5 | NM | NM | NM | NM | NM | 7 | 0 | NM (1-46) | 1 | 6 | 0 |
| [19] | 13 | 61.2(NM) | NM | 7 | 6 | 3 | NM | NM | NM | NM | NM | 9 | 4 | NM | NM | NM | NM |
| [24] | 15 | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM | NM |
| [18] | 13 | 63.5(47-80) | 7 | 6 | 7 | 10 | NM | NM | NM | NM | NM | 10 | 3 | NM (1-12) | NM | NM | NM |

Abbreviations: NM, not mention.

smoking. However, previous studies have reported that 45.6% of patients with PEAC are cigarette smokers [2-14], which suggests that in terms of smoking history, PEAC may be different from the typical pulmonary adenocarcinoma. However, further investigation is required to confirm whether smoking is a risk factor for PEAC.

Clinical characteristics

PEAC is a rare lung cancer with the same morphological and immunohistochemical features as MCRC and has no distinct clinical manifestations. The majority of patients with PEAC mainly present pulmonary manifestations. Cough is the most common initial presenting symptom, and other symptoms include expectoration, hemoptysis, chest tightness, chest pain, dyspnea, fever, night sweats, throat discomfort, headache, fatigue, and enlargement of cervical lymph nodes [4]. None of these symptoms are specific to lung diseases. There are other patients without significant symptoms in daily life who are identified during routine medical examination [5]. No gastrointestinal symptoms (such as hematochezia, nonproductive abdominal pain, diarrhea, and ventosity) were observed during the entire course of the disease [21]. So, a PEAC patient is typically first diagnosed in the respiratory department. PEAC is an aggressive cancer, with early metastatic behavior, and is more likely to have multiple metastases, such as chest wall metastases, dorsal trunk metastases, abdomen metastases, scalp metastases, and brain metastases. Some rare metastases have also been reported. For example, Sun WW et al. [8] described a 62-year-old PEAC patient with pancreatic metastasis, whereas Todisco et al. [22] identified a PEAC case with a rare synchronous cutaneous metastasis. As for the characteristics of lymph node metastasis and site type (central or peripheral), Zhao et al. [3] collected 28 patients with PEAC and found that there were no significant differences between PEAC and primary pulmonary adenocarcinoma in lymph node metastasis and site type (central or peripheral).

Laboratory examination

As a distinct subtype of pulmonary adenocarcinoma, the expression of serum tumor markers—carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9)—were significantly higher in PEAC than in cytokeratin 19 fragments (CYFRA21-1) and neuron-specific enolase (NSE) [3]. CA19-9 showed the highest expression, whereas NSE showed the lowest expression. In addition, consistent overexpression of CEA and CA19-9 appears to be closely associated with primary PEAC pathological progression [2]. However, CEA is a nonspecific tumor marker and CA19-9 has important diagnostic value in gastrointestinal tumor. CYFRA21-1 is currently considered as a tumor marker to detect lung cancer, especially for the diagnosis of NSCLC, whereas NSE is very useful for the diagnosis of small cell lung cancer (SCLC). Therefore, PEAC may be different from classical adenocarcinoma, which suggests that the levels of CEA and CA19-9 should be monitored for diagnosing a patient with PEAC or relapse.

Imaging examination

Chest computed tomography (CT) is an important and basic examination method for lung cancer detection. However, so far, no radiographic features were found in PEAC. Zhao et al. [3] analyzed the lobulation, spiculation, pleural indentation, pleural effusion, and lymphadenopathy of 28 patients with PEAC, and found no differences between PEAC and pulmonary adenocarcinoma. Wang et al. [5] reported the CT results of nine patients in 2014, which demonstrated eight tumors in the right lung, (including seven in the right upper lung and one in the right lower lung) and one in the left lower lobe. These results suggested that PEAC may be typically found in the right upper lobe. After analysis of 28 CT reports of PEAC patients, Zhao et al. [3] found that all tumors presented solid nodules, with no ground-glass opacity (GGO). Gu et al. [11] concluded that nodules are usually confined to the peripheral lung

Table 2
The frequency of immunohistochemical results of PEAC.

| Ref.(country) | IHC results ^a | | | | | |
|---------------|--------------------------|---------------|----------------|---------------|---------------|--------------|
| | CK-7 | Villin | CDX-2 | CK-20 | TTF-1 | Napsin A |
| [2] (China) | 16/18(88.9%) | NM | 13/18 (72.2%) | 17/18 (94.4%) | 7/18(38.8%) | NM |
| [5] (China) | 9/9(100%) | 6/9 (66.7%) | 6/9 (66.7%) | 2/9 (22.2%) | 4/9(44.4%) | 3/9(33.3%) |
| [7] (Japan) | 7/7(100%) | NM | 5/7 (71.4%) | 3/7 (42.9%) | 3/7(42.9%) | 0/7(0) |
| [9] (USA) | 6/6(100%) | NM | 0/6 (0) | 0/6 (0) | 6/6(100%) | NM |
| [10] (Italy) | 46/46(100%) | NM | 46/46 (100%) | 15/46 (32.6%) | 21/46(45.7%) | 21/46(45.7%) |
| [11] (Japan) | 7/8 (87.5%) | NM | 5/8 (62.5%) | 7/8 (87.5%) | 1/8(12.5%) | 0/7(0) |
| [12] (China) | 12/13 (92.3%) | NM | 4/13 (30.7%) | 7/13(53.8%) | 7/13(53.8%) | NM |
| [14] (China) | 10/13 (76.9%) | 10/13 (76.9%) | 8/13 (61.5%) | 8/13(61.5%) | 7/13(53.8%) | 6/13(46.2%) |
| Total | 113/120 (94.2%) | 16/22 (72.7%) | 87/120 (72.5%) | 59/120(49.2%) | 56/120(46.7%) | 30/82(36.6%) |

^a IHC results: Patients who express the biomarker/all patients who tested IHC in the reference (positive frequency).

field in mild pulmonary metastasis. So far, more than 200 cases of PEAC have been reported, and the findings of CT performance are inconclusive in the distribution and morphology of PEAC [2,3,7,15,17-20]. More cases are needed to provide a further understanding of the imaging manifestations of PEAC.

Pathology and immunohistochemistry examinations

Based on the WHO criteria, PEAC is defined as a cancer with cellular structures; predominantly (>50%) resembling those of colorectal adenocarcinoma, namely tall columnar cells with eosinophilic cytoplasm that form irregularly shaped glands (such as alveoli, ethmoidal, papillary) with some glands containing necrotic material [3]. Specifically, PEAC often occurs in the peripheral parts of the lung, and its macroscopic view is similar to that of typical lung adenocarcinoma; wherein the tumor is nodular or lobulated, without capsule, grayish-white or grayish-yellow in sections, with hard texture, and some tumors are accompanied by necrotic tissue. Tumor cells are usually tall and columnar with eosinophilic cytoplasm, brush borders, and fairly large vesicular nuclei with prominent nucleoli. The polarity of nuclei is largely preserved; therefore, they exhibit nuclear palisading, although there is some loss of polarity in cases with moderate differentiation. An intratumoral scar may exist in the central or eccentric position with elastic fiber coagulation, especially in cases with less necrosis. Around those tumor cells, abundant inflammatory cell infiltration can be found. All of the above findings are also observed in MCRC [7]. Most tumors show pure adenocarcinoma morphology, with a small focal squamous cell carcinoma component [10]. A literature review by Nottegar et al. analyzed 46 patients of PEAC and the results indicated the existence of other components besides the intestinal type, including solid (18/46, 39.1% in all cases), mucinous (10/46, 21.7% in all cases), acinar (6/46, 13% in all cases), lepidic (1/46, 2.2% in all cases), papillary (2/46, 4.4% in all cases), micropapillary (1/46, 2.2% in all cases), and pure intestinal morphology (8/46, 17.4% in all cases) [7]. Additionally, pulmonary interstitial fibrosis also appeared frequently in PEAC patients. László et al. [23] described a 65-year-old patient who developed PEAC in his postoperative scar and found advanced interstitial fibrosis in the neighboring lung parenchyma. The same description also appears in Matsushima's report [11].

Immunohistochemistry (IHC) reveals a characteristic of PEAC, which is different from other classical lung adenocarcinomas, that is, it expresses at least one enteric differentiation marker, including caudal type homeobox 2 (CDX-2), cytokeratin (CK 20), and villin. The immunohistochemical results of PEAC were retrospectively analyzed, and the results of IHC are summarized in Table 2. As given in Table 2, the positive percentage of CK-7, villin, CDX-2, CK-20, TTF-1, and napsin A was found to be 94.2% (113/120), 72.7% (16/22), 72.5% (87/120), 49.2% (59/120), 46.6% (56/120), and 36.6% (30/82), respectively. For intestinal markers, villin and CDX-2 were highly expressed, whereas CK-20 was relatively low. A combination of villin and CDX-2 can be used to determine

the primary site of metastatic cancer. If villin and CDX-2 are simultaneously negative, the gastrointestinal origin can be almost excluded. However, both villin and CDX-2 are highly expressed in PEAC, undoubtedly increasing the difficulty in the identification of PEAC and MCRC. For the pneumocyte markers, observed decrease or loss of immunoreactivity for TTF-1 and napsin A indicates that these lesions demonstrate a deviation from other pulmonary phenotypes, although CK-7 expression was retained.

Generally, CDX-2, villin, and CK7 are significantly positive in PEAC, but this does not mean that they are more helpful in the diagnosis of PEAC. Compared with primary pulmonary adenocarcinoma, the expression of TTF-1 tends to be decreased in PEAC, whereas CK7 expression is often retained. This progression of tumor is similar to that of sinonasal intestinal-type adenocarcinomas, which acquires the expression of CDX-2, CK20, and MUC2, while retaining CK7 expression [24,25]. However, it is necessary to exercise caution when using CK7 to diagnose PEAC because some alveolar pneumocytes can be present in metastatic colorectal cancer, which might be judged as CK7-positive. Approximately 10% of well or moderately differentiated colorectal carcinomas express CK7/CK20 [26]. Therefore, after analyzing the expression of CK7 and CDX-2 in 50 colorectal adenocarcinoma samples, Chen et al. [2] proposed that the combination of CK7 + and CDX-2 + has high sensitivity (71.3, 95% CI 63.5–79.1%) and specificity (82%, 95% CI 71.4–92.6%) in the differential diagnosis of primary PEAC than from colorectal adenocarcinoma.

Molecular characteristics

Lung cancer is one of the most common types of cancer, accounting for 13% of all cancers diagnosed worldwide [27]. Although the main cause of lung cancer is smoking, about 25% of patients with lung cancer have no smoking history [28]. Genetic mutations play an important role in lung cancer pathogenesis. Owing to the rarity of PEAC, its molecular characteristics have not been fully studied. Therefore, the mutations in PEAC have not been comprehensively studied. The mutation rates of these genes were determined by collating all of the gene mutation data in the selected articles [2-6,10-13].

As demonstrated in Table 3, we found that the mutation frequency of human epidermal growth factor receptor-2 (*HER2*) in PEAC was 44.4% (8/18), which was higher than that in NSCLC (2%), suggesting that *HER2* may play an important role in PEAC. In addition, the DNA mismatch repair (*MMR*) gene is frequently mutated in PEAC, with 7 of 18 PEAC patients harboring *MMR* mutations [2,12]. As known, microsatellite instability (MSI) is a molecular feature caused by defective *MMR* protein function, which has clinical significance in colorectal and endometrial cancer. Less than 1% NSCLC patients exhibited MSI at single or multiple loci, but it highly occurred in PEAC patients. The high frequency of *MMR* mutations not only makes it more difficult to distinguish PEAC from MCRC, but also leads to a new hypothesis of whether the 1% patients exhibiting MSI in NSCLC are all PEAC patients. Additionally,

Table 3
The frequency of gene mutations in PEAC.

| Ref.(country) | Gene mutation ^a | | | | | | | |
|---------------|----------------------------|-------------|---------------|-------------|------------|---------------|-------------|-------------|
| | HER2 | MMR | KRAS | TP53 | NRAS | EGFR | EML-4ALK | BRAF |
| [2] (China) | 2/5(40.0%) | 4/5(80.0%) | 1/5(20.0%) | NM | 1/5(20.0%) | 1/5(20.0%) | 0/5(0) | 0/5(0) |
| [3] (China) | NM | NM | 10/28(35.7%) | NM | NM | 3/28(10.7%) | NM | NM |
| [4] (China) | NM | NM | 3/15(20.0%) | NM | NM | NM | NM | NM |
| [5] (China) | NM | NM | 0/9(0) | NM | NM | 0/9(0) | NM | NM |
| [6] (China) | NM | NM | NM | NM | NM | 13/30(43.3%) | NM | NM |
| [10] (Italy) | NM | NM | 28/46(60.9%) | NM | NM | 1/46(2.2%) | 6/46(13.0%) | 0/46(0) |
| [11] (Japan) | NM | NM | 1/7(14.3%) | NM | NM | 0/7(0) | NM | 0/7(0) |
| [12] (China) | 6/13(46.2%) | 3/13(23.1%) | 1/13(7.8%) | NM | NM | 5/13(38.5%) | 2/13(15.3%) | 2/13(15.3%) |
| [13] (China) | NM | NM | 9/15(60%) | 5/15(33.3%) | NM | NM | 0/14(0) | NM |
| Total | 8/18(44.4%) | 7/18(38.9%) | 53/138(38.4%) | 5/15(33.3%) | 1/5(20.0%) | 23/138(16.7%) | 8/78(10.3%) | 2/71(2.8%) |

^a Gene mutation: Patients who harbor the mutation/all patients who went through gene test in the reference (mutation frequency).

the high frequency of *MMR* mutations may facilitate the possibility of immunotherapy for PEAC patients in the future.

In general, the mutation rate of kirsten rat sarcoma viral oncogene (*KRAS*) in PEAC was higher than that in primary pulmonary adenocarcinoma, and the positive rate of *KRAS* could reach 38.4%. In addition to the high positive rate, *KRAS* has other characteristics in PEAC. Chen et al. [2] conducted a retrospective study on the mutation data of 129 PEAC cases and confirmed the results of Wang et al. [5], and discovered that the mutations of *KRAS* exons 2, 3, and 4 in PEAC were more common than other mutations, indicating that PEAC may be significantly different from other lung cancer types.

The positive rate of epidermal growth factor receptor (*EGFR*) mutations is much lower than *KRAS*, approximately 16.7% [2,3,5,6,10,11,12]. Notably, the positive rates of *KRAS* and *EGFR* mutations differ between Asians and non-Asians. *EGFR* mutation rate was 30–40% among Asians and 10–20% among non-Asians, whereas the *KRAS* mutation rate was 20–30% in Europe and USA, 8–10% in Asia, and 8.3% in China [1,29]. However, a higher *KRAS* mutation rate and a lower *EGFR* mutation rate were observed in PEAC patients, regardless of their ethnicity [2,4,10,23]. Echinoderm microtubule-associated protein-like 4 gene-*ALK* variant (*EML4-ALK*) is an infrequent oncogenic gene translocation in NSCLC. Nottegar et al. [10] first tested a series of PEACs for *EML4-ALK* translocation by FISH (the rate of translocation was 13.0%) and found no difference in *EML4-ALK* translocation between PEAC and other lung adenocarcinomas. *BRAF* mutation has been rarely found in previous reports. Todisco et al. [22] described a case of PEAC with cutaneous metastasis, and demonstrated two mutations in the metastatic lesion, located in the *SMAD4* and the *FLT3* genes, suggesting that mutations in these two genes may be implicated in tumor metastasis.

In summary, high *HER2*, *MMR*, and *KRAS* mutation rates, and low *EGFR* and *BRAF* mutation rates are observed in PEAC. These mutations hold the promise of more treatment for PEAC patients. But owing to the rarity of PEAC, its mutation frequency needs further study.

Diagnosis and differential diagnosis

Given the common clinical manifestations with other lung adenocarcinomas, a combination of clinical manifestations, laboratory tests, histopathology, IHC, and molecular characteristics are necessary for a definite diagnosis of PEAC. According to the WHO 2015 criteria of primary PEAC [16], an accurate diagnosis needs to meet at least three requirements. First, in terms of histopathology, PEAC should predominantly (>50%) contain cellular structures resembling those of colorectal adenocarcinoma, namely tall columnar cells with eosinophilic cytoplasm that form irregularly shaped glands, with some glands containing necrotic material. Second, in terms of IHC, the tumor must express at least one of the enteric differentiation markers (*CDX2*, *CK20*, and *MUC2*). Third, metastatic colorectal cancer and primary lung adenocar-

cinoma should be excluded. Additionally, if the tumor cells are negative for any intestinal protein markers, it should be termed as “lung adenocarcinoma with enteric morphology” rather than as enteric carcinoma of the lung [5].

PEAC is highly heterogeneous. It is morphologically and immunohistochemically similar to lung adenocarcinoma and MCRC. It can even exhibit the typical pattern of colorectal cancer. Therefore, the differential diagnosis of PEAC from primary lung adenocarcinoma and MCRC is crucial for the diagnosis and treatment of PEAC, since it has a serious impact on the clinical stage, therapeutic strategy, and prognosis.

Differentiation of PEAC from primary lung adenocarcinoma is relatively simple. First, in terms of morphology, the cellular structure of PEAC is similar to that of colorectal adenocarcinoma, with >50% similarity in the composition. Second, CA19-9 and CEA are often expressed in PEAC, but not in other traditional lung adenocarcinomas [2,3]. Third, in terms of immunohistochemistry, specific markers of primary lung adenocarcinomas such as *CK7* and *TTF-1* are also expressed in PEAC (the expression rates in PEAC were relatively lower than in primary lung adenocarcinoma), even in cells of colorectal carcinomas-like (CR-like) areas; but the immunoreactivity for enteric differentiation markers in primary lung adenocarcinomas was essentially restricted to CR-like components [7]. In summary, morphology and immunohistochemistry can help to identify whether the tumor is PEAC or primary lung cancer.

Major advances have been made to distinguish PEAC from MCRC over the last few decades, but the process remains difficult. The identification of PEAC and MCRC involves the following aspects. First, in terms of the medical history, if the patient has a history of colorectal adenocarcinoma, MCRC should be suspected when lung tumors are presented with intestinal differentiation. However, patients with no prior history of colorectal adenocarcinoma may need to be cautiously diagnosed, because the treatment and prognosis of these two diseases are very different [30]. In addition, only one pathological organ is involved in PEAC, whereas MCRC is often accompanied by a history of colorectal cancer or concomitant digestive tract adenocarcinoma at the time of treatment. Besides the clinical symptoms of respiratory system abnormalities, patients also present with digestive tract abnormalities, such as painless bloody stools and abdominal discomfort. In terms of the clinical features, patients with PEAC generally do not have gastrointestinal symptoms (such as hematochezia, nonproductive abdominal pain, diarrhea, and ventosity) during the entire course of the disease [21].

In terms of pathology, Matsushima et al. [11] found that some pathological manifestations of PEAC include interstitial pneumonia with the usual interstitial pneumonia (UIP) pattern in the background lung tissue, whereas this pathological feature is rarely found in MCRC. Different expressions of immune markers in lung tissue and intestinal tissue are also commonly used to distinguish between PEAC and MCRC. The immunohistochemical distinction of PEAC from MCRC has become a research hotspot. *TTF-1*, surfactant apoprotein-A (SP-a), *CK7*, and *CK20* are commonly used as markers to determine whether the tumor is a lung tissue

[31-36]. CDX-2 is a highly sensitive marker for determining whether the tumor is a lung tissue [37,38], as it is specifically expressed where a majority of enteric adenocarcinoma are located [39,40]. Moreover, Ueno et al. [41] discovered a new aspartic protease named napsin A, which is expressed in type II alveolar epithelial cells and could be a useful marker for the diagnosis of primary lung adenocarcinomas. However, PEAC can express immune markers related to pulmonary and intestinal differentiation, so there are limitations to use immune markers alone to distinguish PEAC from MCRC. Another characteristic of PEAC is histological heterogeneity, wherein the tumor samples composed of only one component are relatively rare. This requires pathologists to obtain multiple samples from a tumor, and diagnosis is challenging for a single sample or a pure component example.

PEAC patients tend to exhibit higher *HER2*, *MMR*, and *KRAS* mutation rates and lower *EGFR* mutations rate. In addition, Matsushima et al. [11] recommended the use of β -catenin and *SATB2* to identify PEAC and MCRC. Powell et al. [42] reported that 60% of colorectal adenocarcinomas had *APC* mutations. The degradation of β -catenin protein is required for the participation of adenomatous polyposis coli (*APC*), so the inactivation of *APC* mutation will lead to the nuclear accumulation of β -catenin protein in the nucleus. Mutations in β -catenin also cause the accumulation of nuclear/cytoplasmic β -catenin, which is common in colorectal adenocarcinomas [43]. However, the mutation of β -catenin in pulmonary adenocarcinomas is uncommon and occurs only in 4–15% of cases [44,45]. *SATB2* is expressed in 86–93% of primary colorectal adenocarcinomas and 81–94% of MCRCs [46,47], but in only 10% of conventional pulmonary adenocarcinomas [47]. The use of colonoscopy, CT, and PET-CT to exclude colorectal lesions is also important for distinguishing between PEAC and MCRC.

Based on the above findings, the differentiation between PEAC and primary lung adenocarcinoma is relatively simple; but the differentiation between PEAC and MCRC requires a combination of clinical manifestations, laboratory tests, pathology, immunohistochemistry, and mutational analysis.

Treatment

The treatment of PEAC has not been specifically reported in previous studies. The present treatment strategy is similar to that of NSCLC. A comprehensive treatment regimen consisting mainly of surgical resection, supplemented by chemotherapy, radiotherapy, and targeted therapy should be adopted according to different clinical stages. Although many case reports and studies mentioned that different gene mutations were detected in PEAC patients, they did not indicate whether the PEAC patients received targeted therapy.

Surgical resection is the preferred treatment for early PEAC patients, including lobectomy, pneumonectomy, and segmental resection. Zhao et al. [3] summarized the detailed surgical procedure and prognosis of 28 patients (all of them underwent systematic mediastinal lymphadenectomy) as follows: 24 patients underwent lobectomy; of which five patients died within 1–20 months after surgery, and the remaining patients survived, with the longest survival being 30 months. Three patients underwent segmentectomy and lived for 19–29 months. One patient underwent unilateral pulmonary resection and lived for 30 months. However, owing to the limited data, the prognosis of PEAC remains unclear.

Given the similarities between PEAC and colorectal adenocarcinoma, chemotherapy regimens can be divided into two types. One chemotherapy regimen is for non-small cell lung adenocarcinoma, which includes carboplatin combined with paclitaxel; the other chemotherapy regimen is for colorectal adenocarcinoma, which includes oxaliplatin, irinotecan, and fluorouracil [48,49]. The most commonly used regimen is carboplatin combined with paclitaxel and although this is the most common chemotherapy regimen for PEAC, the only successful case reported till now had to undergo four cycles of pemetrexed and carboplatin [18]. It is theoretically possible to apply the chemotherapy for MCRC for

the treatment of PEAC, but Garajová et al. and Lin et al. found that chemotherapy regimens for MCRC had no significant effect on PEAC [18,50]. There are very few reports on the treatment of distant metastasis. Todisco et al. [22] reported a patient with multiple metastases from PEAC who received systemic treatment with pemetrexed-cisplatin and bisphosphonates, with radiotherapy on the pelvis (20 Gy divided into five fractions), after which his bone pain was significantly relieved. This offers insights into the treatment of bone pain in terminal patients, but whether it is effective in the majority of patients needs to be tested in the clinic.

Targeted therapy is indispensable in the comprehensive treatment for lung adenocarcinoma and has been developing rapidly in recent years. However, mutational analyses have exhibited that the positive rate of *EGFR* mutations is relatively low in PEAC compared with conservative pulmonary adenocarcinoma. Therefore, it may be unreasonable to use *EGFR* tyrosine kinase inhibitors in the treatment of PEAC [4]. Moreover, owing to the high proportion of *HER2* mutation in PEAC patients, recent studies have demonstrated that pyrotinib, poziotinib, and DS8201a have better efficacy in NSCLC patients harboring *HER2* mutation. With the rapid development of targeted therapy for non-small cell lung cancer, drugs targeting *KRAS* mutations may appear in the future.

Reck et al. [51] found that in advanced NSCLC patients with at least 50% of tumor cells expression programmed cell death ligand1 (PD-L1), treatment with pembrolizumab had a better therapeutic effect than platinum-based chemotherapy. Therefore, these patients will benefit from the treatment with pembrolizumab, but the immunostaining of PD-1 lacks uniform standards. In 2015, Rizvi et al. [52] found a significant correlation between the tumor mutational burden (TMB) and the sensitivity of NSCLC patients to PD-1 blockade. Based on this finding, Chen et al. [2] first analyzed the TMB of PEACs and found that the nonsynonymous TMB of primary PEAC was much higher compared with traditional lung adenocarcinoma, suggesting that checkpoint blockade immunotherapy might be a useful treatment for PEAC. Besides, as given in Table 3, PEAC has a high frequency of *MMR* mutation, which may be a useful biomarker for the treatment of PD-1 [2,12].

Prognosis

PEAC has low morbidity, and the majority of published reports are individual cases, so its prognosis is not well understood. PEAC is an invasive tumor that can rapidly metastasize; therefore, early diagnosis is crucial for the prognosis. Clinical factors that influence the prognosis of PEAC remain unclear, and therefore, the prognosis of PEAC can be only be analyzed from the follow-up time. Chen et al. [2] analyzed the prognosis of 18 PEAC patients (12 were stage I/II and six were stage III/IV); among which three patients died, two patients were lost to follow-up, and the remaining 13 patients survived. The median survival time was 31 months. Zhao et al. [3] followed up with 28 PEAC patients; among which five patients died (the follow-up time was 1–30 months), 19 survived (the follow-up time was 13–31 months), and four were lost to follow-up. Gu et al. [4] followed up with 23 patients for 56 months; among which six patients died, six were lost to follow-up, and 11 patients survived. The present study used follow-up survival time to analyze the prognosis of patients at different clinical stages and found that the prognosis of patients with PEAC is directly related to their clinical stage. The survival time of stage III or IV patients with PEAC ranged from 0 to 9 months, and the survival times of stage I or II patients may reach from 1 to 27 months [2-14]. However, there were few cases involved that still needed many details for further exploration, for example, whether different therapy will have an impact on the prognosis of PEAC. Given the small number of reported cases, a more detailed prognosis is not possible. More studies are needed in the future on the relationship between the clinicopathological features, mutations, and prognosis of PEAC.

Conclusion

PEAC was first described by Tsao in 1991, and very few cases have been reported since then. PEAC is a rare variant of lung adenocarcinoma and is an invasive tumor. Hence, accurate and early diagnosis plays a critical role in the treatment and prognosis of PEAC patients, which has huge challenges. Its clinical manifestation is primarily lung manifestations, and there is no distinct difference from ordinary lung adenocarcinoma. Its pathological and immunological features are similar to those of MCRC, but are characterized by high expressions of CK-7, villin, and CDX-2. Accurate diagnosis requires a combination of clinical manifestations, laboratory tests, histopathology, immunohistochemistry, and mutational status. Treatment of PEAC has been rarely reported. There are no specific guidelines for the treatment of PEAC, and the present treatment strategy is similar to that of NSCLC. Surgical treatment is the main treatment in the early stage, and chemotherapy and radiotherapy can be supplemented for advanced patients. Using EGFR tyrosine kinase inhibitors in the treatment of PEAC is unreasonable. The high mutation rates of *KRAS* gene and *HER2* in PEAC patients may provide new directions for future studies. Recent studies have demonstrated that pyrotinib, poziotinib, and DS-8201a demonstrate good antitumor activity and safety in patients with *HER2* mutation, which may become an effective treatment for PEAC patients with *HER2* mutation. A new drug targeting *KRAS* mutations may also be developed in the future, which would be a huge step forward for PEAC treatment. Based on the high TMB and MMR mutation rates in PEAC patients, immune checkpoint inhibitors may also provide a longer survival for these patients. At present, there are few reports on the prognosis of PEAC, and the relationship between tumor location, immunohistochemical results, tumor mutation, and the prognosis of PEAC remains unclear. Extensive data is needed for systematic prognostic statistics, which can guide clinical treatment. The present information about PEAC is just the tip of the iceberg, so extensive studies are needed to make further progress in PEAC in the future.

CRedit authorship contribution statement

Jiali Gong: Writing – original draft, Writing – review & editing, Investigation. **Ying Fan:** Visualization, Formal analysis. **Hongyang Lu:** Conceptualization, Supervision.

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Declaration of Competing Interest

The authors report no conflicts of interest in this study.

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