



Pulmonary enteric adenocarcinoma: a literature review

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Abstract: Pulmonary enteric adenocarcinoma (PEAC) is an extremely rare type of non-small cell lung cancer (NSCLC) with a histologic pattern that mimics metastatic colorectal cancer (MCC). The main clinical symptoms in PEAC patients are dyspnoea, coughing, hemoptysis, and chest and back pain. The first article about PEAC appeared in 1991 in the form of a case report. As a variant of invasive lung carcinoma, only a small number of case reports and clinical research studies have been carried out, and the only one guidance on diagnosis and treatment is the WHO Tumor Classification book. It is important for doctors to distinguish PEAC from MCC to extend survival time and improve the quality of life. We reviewed the existing literature regarding the diagnosis, treatment, and prognosis of PEAC to provide some valuable clinical references.

Keywords: Pulmonary carcinoma; enteric; diagnosis; treatment; prognosis

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Introduction

The first case of pulmonary enteric adenocarcinoma (PEAC) was described in 1991 by Tsao and Fraser who reported on a lung adenocarcinoma with morphologic features similar to intestinal (*Figure 1*) (1). In 2011, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma announced for the first time that PEAC, along with invasive mucinous adenocarcinoma (formerly mucinous BAC), colloidal adenocarcinoma, and fetal adenocarcinoma (low and high grade) were to be classified as variants of invasive adenocarcinoma of NSCLC. The following pathologic criterion for PEAC was also set out: if the intestinal differentiation component in lung adenocarcinoma exceeds 50%, the tumor can be classified as PEAC (2). Despite PEAC being subsequently proposed in the 2015 World Health Organization classification,

due to the rarity of the disease, systematic guidance or recommendations regarding its diagnosis, treatment, and prognosis are lacking (3). Therefore, collecting, collating and analyzing data relating to the imaging, laboratory investigation, pathology, immunohistochemistry (IHC), clinical treatment, and prognosis of PEAC, would be of great significance.

Methods

We searched for articles about PEAC from PubMed, CNKI for the words *pulmonary*, *lung*, *enteric*, *intestinal*, *difference* and *adenocarcinoma*. All the data obtained from existing literatures were collated by Microsoft Office application.

Clinical pathological features

Clinical characteristics of PEAC were similar to that of typical lung cancer (4). Most patients with PEAC complain

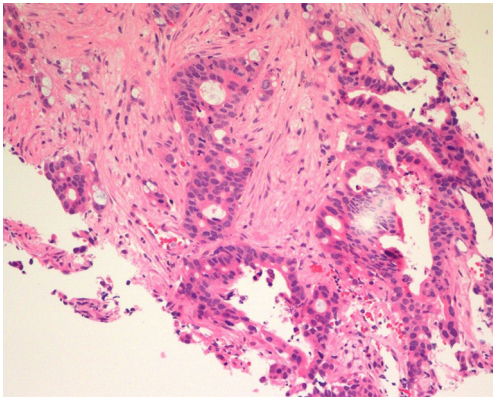


Figure 1 Histomorphologic features of pulmonary enteric adenocarcinoma: (I) high columnar cells with eosinophilic cytoplasm that are arranged in irregular glandular lumens with central necrosis; (II) a tall or oval nucleus with pseudo-stratification. (H&E, $\times 200$)

of respiratory symptoms such as coughing, expectoration, chest pain, dizziness, hemoptysis, fever, bronchitis, and other related discomfort (1,5-21). Almost 51.2% (22/43) of the patients in these literatures went to the doctor for coughing and 20.9% (9/43) for chest or back pain. The probability of hemoptysis, fever, and cystic mass were relatively lower, at about 16.3% (7/43), 11.6% (5/43), and 11.6% (5/43) respectively (1,6,8,10-17,19-21). Only a small number of patients from abnormal lesions detected on health examinations, at about 4.7% (2/43).

Date in literatures indicated that PEAC affected more males, with a male-to-female ratio of about 1.23. The age of onset was concentrated in middle-aged and older patients aged 60–72 years old, with a median age of 65 years old (Table 1). However, it is worth noting that PEAC can also be suffered by some young adults. In the articles we searched, there were approximately 8.1% (8/99) patients <45 years old. Although this accounts for only a small proportion of the patients in our study, it should not be overlooked.

Bian *et al.* found that 76.9% of PEAC patients had a history of smoking, which suggests that smoking may be a risk factor for this type of pulmonary adenocarcinoma (9). Currently, there is no literature that studies the relationship between smoking and PEAC or reveals a clear correlation between them. By observing the data distribution in the literature in this study, we found that 46.1% (71/154) of PEAC patients had a history of smoking, which is less definitive than the results of Bian *et al.* but still suggests

that there may be a certain degree of correlation between smoking and PEAC.

Imaging features

PEAC almost always shows in CT and PET/CT as an abnormal mass in the lung. Whether by CT or PET/CT imaging, primary lesions and metastases of PEAC can be detected. Metastases from PEAC can be found in the lymph nodes, bones, liver, adrenal glands, subcutaneous soft tissue, and pancreas. Furthermore, invading tumor tissues can be found in the airways, pleura, chest wall, and in blood vessels (1,5,6,8,9,11,12,14-16,18,19,21,24,26,28,30-32). The findings of studies in this area have been significantly different. Among them, Bian *et al.*'s study showed that PEAC was more inclined to invade the pleura and airways, with a rate of 38.5% (5/13) and 46.2% (6/13), respectively. In comparison, the proportion of lymph node metastasis was only about 10% (1/10), which was relatively limited (9). Wang *et al.* found that the main site of metastasis of PEAC was the lymph nodes, with a rate of 44.4% (4/9), whereas the percentages of vascular and pleural infiltration were relatively lower, with both about 22.2% (2/9), and there was no evidence regarding airway invasion (16). Wang *et al.*, in another paper, suggested that vascular invasion occurred more frequently, in approximately 40% of cases (2/5), whereas for pleural or lymph node metastasis, the proportion was approximately 20% (1/5) (18). It can be suggested that PEAC is a carcinoma with high malignancy and poor prognosis due to its tendency of lymph node metastasis and vascular/airway/pleural invasion.

PEAC tends to present on chest imaging as a single lesion, although multiple lesions have also been noted (9,14,27,33,34). We organized and analyzed all data in the current literature (Table 1). The results showed that the lesions were more commonly distributed on the right lung tissues, and the ratio of lesions located in the right lung in comparison to the left lung was about 66:49 (1,8-13,15-17,19-23,25,27,30,31,34-36). The sites of PEAC that lesions located were right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe. The rate of each location mentioned previously was about 35.0% (36/103), 4.9% (5/103), 18.4% (19/103), 22.3% (23/103), 20.4% (21/103), respectively (1,8-10,12,13,15-21,23,25,27,30-35). It was not clearly that the ratio about central lung carcinomas and the peripheral ones.

Table 1 Clinicopathologic features of patients with pulmonary enteric adenocarcinoma

References	Gender		Smoking status		Age in years		Site		Tumor size (cm)	
	F	M	Yes	No	Median	Range	R	L	Median	Range
Bian <i>et al.</i> (9)	7	6	10	3	60	47–80	7	6	2.5	0.5–11.0
Chen <i>et al.</i> (22)	12	6	4	14	NA	55–76	9	9	3.1	1.1–6.6
Zhang <i>et al.</i> (23)	6	7	3	10	NA	NA	5	8	NA	NA
Gu <i>et al.</i> (5)	6	9	NA	NA	NA	44–72	NA	NA	NA	NA
Sato <i>et al.</i> (24)	1	4	5	0	72	51–77	NA	NA	2.6	1.7–3.9
Inamura <i>et al.</i> (25)	1	6	NA	NA	NA	NA	4	3	3.4	1.7–5.0
Wang <i>et al.</i> (16)	5	4	6	3	63	34–74	8	1	3.0	1.5–6.0
Yousem <i>et al.</i> (21)	4	2	6	0	71.5	57–82	5	1	2.9	1.5–7.0
Feng <i>et al.</i> (26)	21	9	7	23	NA	NA	NA	NA	NA	NA
Zhao <i>et al.</i> (8)	6	22	8	20	66.5	43–82	15	13	3.4	1.0–7.0
Matsushima <i>et al.</i> (27)	2	5	5	2	70	41–77	4	4	4.3	1.5–11.5
Wang <i>et al.</i> (18)	2	3	3	2	63	56–74	4	1	3.5	2.0–5.0
Lin <i>et al.</i> (28)	4	2	NA	NA	NA	25–78	NA	NA	NA	NA
Xu <i>et al.</i> (7)	2	13	NA	NA	NA	45–81	NA	NA	NA	NA
Jurmeister <i>et al.</i> (29)	3	4	7	0	56	46–78	NA	NA	NA	NA
GCR (1,6,10-15,17,19,20,30-35)	9	10	7	6	62	24–81	10	5	2.8	1.0–5.0
Total	91	112	71	83	65	24–82	71	51	3.0	0.5–11.5

GCR: Group of Case Report; F, female; M, man; R, right; L, left; NA, not available.

Furthermore, the size of lesions was not fixed, with diameter size ranging from 0.5 to 11.5 cm, and a median diameter of 3.5 cm (1,8,9,12,16–22,24,25,27,30,31,34,35,37). A number of the existing case reports and research studies mentioned the imaging-based findings of PEAC. Bian *et al.* suggested that imaging of PEAC lesions showed them to have regular morphology with clear borders. Some lesions were lobulated, and a few were burr-like, and, occasionally, they were associated with pleural indentation, although there were no bronchial signs (9). In another study, the authors pointed out that the CT images showed the PEAC lesions to be more lobulated, with pleural indentation, however, the burr-like changes were not prominent (8). In addition, the study also suggested that solid nodules are more common than partially solid lesions or ground-glass nodules. Although PEAC has CT-prone manifestations, the study found no statistically significant difference in metastatic colorectal cancers (MCC) and PEAC (8). Lesions in PEAC always manifested as solid or part-solid nodules or masses (5,8,10,12–15,17,19,30,33–35), with boundaries

clearly, which were similar to typical lung adenocarcinoma (4).

The application of PET/CT in PEAC was limited to providing information on lesion metabolism. Patients who underwent PET/CT examinations found that lesions had a high uptake of imaging agent, and the SUV max ranged from 2.0 to 12.72. Most of the primary lesions had a higher SUV max than the metastases in PEAC (6,12–14,16,19,20,27,28,30,31,33).

Clinical laboratory

Laboratory tests for tumor biomarkers may be helpful in the diagnosis of PEAC (Table 2) (5,6,12,14,20,22,26). Almost 68.2% (45/66) of the patients in the included literature found to have an elevated CEA level. Although this marker had a high sensitivity and could be used to monitor the patient's clinical course (14), it was not useful for distinguishing PEAC from MCC (26). The positive rates of CA125 and CA19-9 were relatively lower, at about

Table 2 The percentage of elevated tumor biomarkers in patients with pulmonary enteric adenocarcinoma

References	CEA	CA19-9	CA153	CA125	CYFRA21-1	TSGF	NSE
Chen <i>et al.</i> (22)	6/18	9/18	NA	NA	2/18	NA	0/18
Gu <i>et al.</i> (5)	10/14	5/10	NA	5/10	NA	NA	NA
Feng <i>et al.</i> (26)	28/30	NA	NA	NA	NA	NA	NA
Sun <i>et al.</i> (12)	1/1	1/1	NA	NA	NA	NA	NA
Maeda <i>et al.</i> (20)	0/1	NA	NA	NA	0/1	NA	NA
Lin <i>et al.</i> (14)	1/1	0/1	1/1	NA	NA	NA	NA
Gu <i>et al.</i> (6)	0/1	0/1	NA	NA	0/1	1/1	0/1
Total	46/66	15/31	1/1	5/10	2/20	1/1	0/19
Percentage	69.7	48.4	100	50	10	100	0

50% (5/10) and 48.4% (15/31), respectively. CYFRA21-1 and NSE were seldom positive, about 10% (2/20) and 0% (0/19), respectively. Some markers were tested only once and were found to be positive, including CA153 and TSGF. Further clinical research is needed so that more accurate data about these markers may be gathered.

Pathology

The histopathology of PEAC has its own unique pathological manifestations (37). The histopathology of typical lung and intestinal adenocarcinoma both include: (I) high columnar cells with eosinophilic cytoplasm, (II) glandular or sieving structures with eosinophilic cytoplasm and lumen necrosis, (III) a tall or oval nucleus with pseudo-stratification that aligns inflammatory cells and fibrotic hyperplastic mesenchymal cells, (IV) high columnar cells that are arranged in irregular glandular lumens with central necrosis, (V) brush borders, and (VI) irregular necrotic areas. Satoh *et al.* suggested that PEAC cytology cells tended to be medium and large cell clusters, with no or low overlapping, weak to moderate cohesiveness, palisading, and the glandular arrangement was approximately 22–25%. What's more, there was a high proportion of nuclear irregularities, approximately 71.4%, with nuclear membrane thickening, pale nuclear chromatin staining, and a structure that was finely granular to finely reticular of chromatin. Conventional cytology could thus hold statistical value for distinguishing between lung-intestinal adenocarcinoma, lung adenocarcinoma, and colorectal lung metastases (24).

Although PEAC has its own pathological features, it could not be completely distinguished from lung MCC

by histopathology alone. A case report presented that the tumor histology was reviewed by pathologists from four different institutions. Although colonoscopy, gastroscopy, clinical characterization, medical history, and various imaging studies did not support the presence of colorectal cancer, these four institutions maintained that the primary tumor was highly likely to be a metastatic malignant tumor of the digestive tract, and it was finally confirmed to be a lung-intestinal adenocarcinoma during the diagnosis and treatment (14).

IHC

The IHC of PEAC is of great significance. All papers about PEAC gave a mass of data regarding its IHC (Table 3). The immunohistochemical markers employed in these articles were CK7, TTF-1, CK20, CDX2, Villin, NapsinA, and MUC2. We compiled all the case reports into a group. The positive rates of each index mentioned previously range from 20–100%, 12.5–100%, 0–100%, 0–100%, 66.7–100%, 0–80% and 0–80%, respectively. The median positive rate of these indexes was approximately 87.5%, 42.9%, 41.5%, 71.8%, 86.7%, 26.7% and 32.6%, respectively. We also analyzed the average positive rate of each indicator, and the results were approximately 84.3%, 41.3%, 46.0%, 76.0%, 83.7%, 33.1%, and 36.0%, respectively. Some articles mentioned that Surfactant A (SP-A), Surfactant B, MUC1, MUC6, MUC5, and other immunohistochemical indicators had a positive performance, but these studies were too small to give statistically significant information about the sensitivity and specificity of these indicators. Further clinical research is needed.

Table 3 Expression of immunohistochemical markers in pulmonary enteric adenocarcinoma

References	CK7	TTF-1	CK20	CDX-2	Napsin A	Villin	SP-A	MUC2	MUC5	MUC 1	MUC6
Bian <i>et al.</i> (9)	10/13	7/13	8/13	8/13	6/13	10/13	NA	NA	NA	NA	NA
Jurmeister <i>et al.</i> (38)	11/15	2/15	8/15	15/15	NA	NA	NA	NA	NA	NA	NA
Chen <i>et al.</i> (22)	16/18	7/18	17/18	13/18	NA	NA	NA	NA	NA	NA	NA
Zhang <i>et al.</i> (23)	13/13	7/13	7/13	4/13	NA	NA	NA	NA	NA	NA	NA
Inamura <i>et al.</i> (25)	7/7	3/7	3/7	5/7	0/7	NA	1/7	3/7	NA	NA	NA
Wang <i>et al.</i> (16)	9/9	4/9	2/9	6/9	3/9	6/9	NA	4/9	NA	NA	NA
Yousem <i>et al.</i> (21)	6/6	6/6	0/6	0/6	NA	NA	NA	1/6	2/6	6/6	1/7
Nottegar <i>et al.</i> (37)	46/46	21/46	15/46	46/46	21/46	NA	21/46	15/46	NA	NA	NA
Feng <i>et al.</i> (26)	NA	NA	9/30	26/30	NA	26/30	NA	NA	NA	NA	NA
Zhao <i>et al.</i> (8)	18/27	10/28	9/26	16/28	6/26	25/28	NA	NA	NA	NA	NA
Matsushima <i>et al.</i> (10)	7/8	1/8	7/8	5/8	0/7	NA	NA	2/7	2/7	NA	NA
Wang <i>et al.</i> (18)	5/5	3/5	0/5	3/5	4/5	NA	NA	4/5	NA	NA	NA
Lin <i>et al.</i> (28)	1/5	1/6	5/5	5/5	1/4	5/5	NA	NA	NA	NA	NA
Xu <i>et al.</i> (7)	13/15	7/15	6/15	12/15	4/15	NA	NA	1/2	NA	NA	NA
Jurmeister <i>et al.</i> (29)	5/7	1/7	2/7	7/7	NA	NA	NA	NA	NA	NA	NA
GCR (5,6,10,11,13,14,17,19,20,30-35)	10/17	6/17	12/16	13/15	1/7	5/7	NA	1/4	1/2	1/3	NA
Total	177/211	86/213	110/239	184/240	46/139	77/92	22/53	31/86	5/15	7/9	1/7

Immunohistochemical markers play important roles in distinguishing PEAC from usual lung adenocarcinoma and MCC. The positive rates of immunohistochemical markers such as villin, CK20, and CDX2 in PEAC were significantly higher in PEAC than in MCC ($P < 0.05$) (26). Elevated CK7 in PEAC is important in distinguishing it from MCC (23). Relatively speaking, CK20 and TTF-1 are less accurate than CK7 but also have statistical significance. Some tumor markers, such as CK7+ and CDX2+, when applied in combination, improved the sensitivity (71.3%) and specificity (82%) in distinguishing between PEAC and MCC (22).

Recently, many scholars have begun to explore alternative methods for the differential diagnosis of PEAC and MCC. Jurmeister *et al.* reported that DNA methylation profiling analysis could reliably distinguish between PEAC and MCC (38). Bian *et al.* suggested that the combination of CDH17 and SATB2 can improve the sensitivity (76.92%) and specificity (100%) of the diagnosis of PEAC (9), and this kind of combination could be used as the best marker for distinguishing PEAC from MCC.

Gene mutation

Gene mutation detection plays a significant role in personalized cancer therapy. The genes that have been frequently detected in PEAC are KRAS, EGFR, BRAF, and ALK. The mutation rate of these genes was determined by collating all of the gene mutation data in the selected articles (5-8,14-16,22,23,26,27,29-33,35,37-39). We found that the mutation ratio of each gene was about 44.2% (68/154), 14.9% (26/175), 2.5% (2/79) and 8.3% (9/108) (Table 4). In view of the differences in the detection of mutations among different genes, we compiled the average of all gene mutation rates and found that the average mutation rates of the genes mentioned above were about $47.1\% \pm 33.7\%$, $12.4\% \pm 15.7\%$, $2.6\% \pm 6.3\%$, and $5.1\% \pm 7.1\%$, respectively. It is evident that the KRAS gene in PEAC has a high mutation rate of about 40–50%. Unfortunately, there were scarcely any achievements to use guided-therapies to target this type of gene mutation (40).

The MET and ROS1 gene mutations were detected in one study, and the result suggested that neither of these genes was mutated (38). Zhang *et al.* performed a study that

Table 4 The frequency of gene mutations in pulmonary enteric adenocarcinoma

References	KRAS	EGFR	BRAF	ALK	NRAS	TP53	PIK3CA	E2	M2	P2
Jurmeister <i>et al.</i> (38)	9/15	NA	NA	0/14	NA	5/15	NA	NA	NA	NA
Chen <i>et al.</i> (22)	1/5	1/5	0/5	0/5	1/5	NA	NA	NA	NA	NA
Gu <i>et al.</i> (5)	3/15	1/15	NA	0/15	NA	NA	NA	NA	NA	NA
Garajová <i>et al.</i> (31)	2/2	0/2	NA	0/2	NA	NA	NA	NA	NA	NA
Zhang <i>et al.</i> (23)	1/13	5/13	2/13	2/13	NA	NA	NA	6/13	2/13	1/13
Wang <i>et al.</i> (16)	0/9	0/9	NA	NA	NA	NA	NA	NA	NA	NA
Nottegar <i>et al.</i> (37)	28/46	1/46	0/46	6/46	NA	NA	NA	NA	NA	NA
Stojisic <i>et al.</i> (32)	1/2	NA	NA	NA	NA	NA	NA	NA	NA	NA
Feng <i>et al.</i> (26)	NA	13/30	NA	NA	NA	NA	NA	NA	NA	NA
Zhao <i>et al.</i> (8)	10/24	3/27	NA	NA	NA	NA	NA	NA	NA	NA
Matsushima <i>et al.</i> (27)	1/6	0/6	0/6	NA	NA	NA	NA	NA	NA	NA
Nottegar <i>et al.</i> (39)	4/8	0/8	0/8	1/8	0/8	NA	1/8	NA	NA	NA
Jurmeister <i>et al.</i> (29)	6/7	NA	NA	NA	NA	3/7	NA	NA	NA	NA
GCR (6,7,14,15,30,33,35)	2/2	2/14	0/1	0/5	NA	NA	NA	NA	NA	NA
Total	68/154	26/175	2/79	9/108	1/13	8/22	1/8	6/13	2/13	1/13
Frequency	44.2	14.9	2.5	8.3	7.7	36.4	12.5	46.2	15.4	7.7

found PEAC had different degrees of *ERBB2*, *MSH2* and *PMS2* gene mutations (23). The authors found, by analyzing the mutation spectrum, that PEAC and NSCLC had similar mutational characteristics. Compared with CRC and MCC, PEAC had its own unique mutational characteristics, and it was thought that this might be another classification model that integrates IHC markers and genetic markers to diagnose PEAC accurately. However, in this study, the proportion of *KRAS* gene mutations was found to be only 7.7% (1/13), in contrast to the results mentioned above. Therefore, although this classification method had statistical significance, further examination is required.

Treatment and prognosis

At present, the principal treatment methods for PEAC are surgery and systemic chemotherapy. Although many of the selected case reports and studies mentioned that different genetic mutations were detected in PEAC patients, there was scarcely any evidence of PEAC patients receiving targeted therapy. Patients at all clinical stages might undergo surgical resection if their circumstances permitted. The data in literatures indicated that the rate

about surgical resection of clinical stage I, stage II, stage III, and stage IV was about 100% (41/41), 100% (20/20), 100% (9/9), and 25% (1/4), respectively (1,8,9,11,14-17,19-21,24,27,34,36). Chemotherapy is the main adjuvant treatment for PEAC, and the most commonly used regimen is carboplatin combined with paclitaxel, which is typical adjuvant chemotherapy for primary lung adenocarcinoma (2,3). Only a few articles mentioned that chemotherapy had been applied to PEAC patients (10,11,14,15,19,30,31,36). The survival time for clinical stage IV patients after chemotherapy treatment was wide, ranging from 2 to 12 months, which may be related to the patient's own physical state. Nevertheless, it was undeniable that the application of carboplatin and paclitaxel had a positive effect on the treatment of PEAC. Garajová *et al.* and Lin *et al.* found that the chemotherapy regimens for MCC were not suitable for PEAC (14,31). Lin *et al.* presented a patient who was initially diagnosed as MCC, and there were no signs to suggest the tumor had responded to MCC chemotherapy (14). The study of Garajová *et al.* described a patient who was correctly diagnosed with PEAC at an earlier stage, but as the relationship between PEAC and colorectal cancer was not correctly acknowledged, doctors first prescribed a

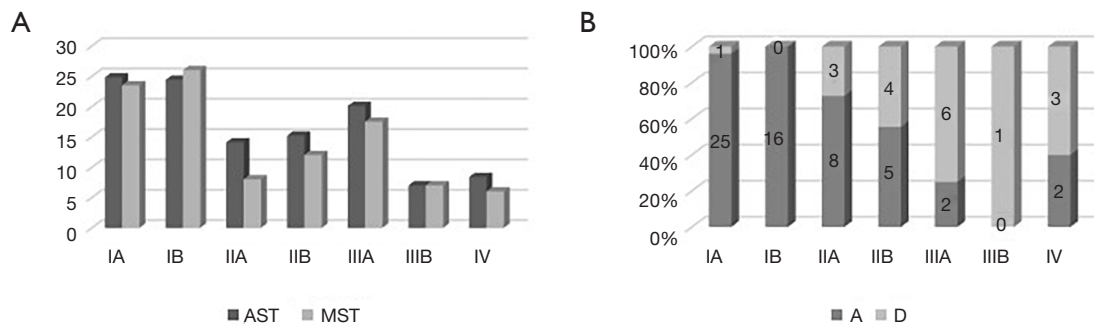


Figure 2 Survival data of patients with pulmonary enteric adenocarcinoma. Average survival time (AST) and median survival time (MST) were stratified according to clinical stages (A). The distributions of alive and deceased patients were stratified according to clinical stages (B). A, Alive; D: Dead.

treatment of capecitabine/oxaliplatin/bisphosphonate (31) and, as a result, the disease failed to be controlled.

As there were no studies or case reports that involved PEAC patients at various stages of chemotherapy who had also received surgery, it was impossible to compare the efficacy of chemotherapy treatment alone with that of the combined treatment of surgery and chemotherapy.

The prognosis of PEAC is directly related to patients' clinical stages. We used follow-up survival time to analyze the prognosis of patients at different clinical stages. For comparison, we treated the follow-up time as the survival time of these live patients. These patients' clinical stages were classified into IA, IB, IIA, IIB, IIIA, IIIB, and IV. We found that the median and mean survival times of patients in different clinical stages were alike, at approximately 23.5 and 24.8, 26.0 and 24.4, 8.0 and 14.1, 12.0 and 15.2, 17.5 and 20.1, 7.0 months (only one patient in the data had a stage of IIIB), and 6.0 and 8.4 months, respectively (*Figure 2A*). From these data, it is evident that the higher the patient's stage, the shorter their survival time was. However, the survival time of patients in stage IIIA was longer than that in patients with stage IIA and IIB. There may be two influencing factors for this. First, the patients in stages I and II were different from those in stages III and IV, and the vast majority of patients' follow-up deadlines did not exceed their overall survival time. Indeed, many patients remained alive at the end of the follow-up time, which shortened the survival time of early-stage patients (*Figure 2B*). Second, there were too few cases in stage III to accurately calculate the prognosis (*Figure 2B*). Overall, early-stage patients (stages I and II) had longer survival times than those in at an advanced stage (stages III and IV) significantly.

The latest study which was about gene mutations suggested that new treatment strategies for patients with PEAC might be not far away in the future (29).

Summary

As a variant of invasive pulmonary adenocarcinoma, PEAC has malignant characteristics in imaging, pathology, and IHC, as well as a poor prognosis. Taking advantage of imaging examinations might help to prolong the patient survival times through early diagnosis and treatment, as patients at stage I survived for up to more than 2 years, while the survival times of patients at stage IV did not surpass much more than 8.5 months. Exact diagnosis is extremely important. However, to get the accurate diagnostic result needs radiology images, endoscopy, histopathology and IHC, and clinical evaluation to exclude the possibility about colorectal primary. To make precise diagnosis and treatment, carcinoma markers (such as CEA, CA125, and CA199), pathology, and IHC (including CK7, TTF-1, CK20, CDX2, villin, Napsin A, and MUC2) are needed. There are no specific guidelines for management of patients with PEAC, but general principles for typical lung adenocarcinoma are still applicable. Although the selected literature did not mention the use of targeted medicines, approximately 40–50% of patients with PEAC had the *KRAS* gene mutation. We might hold the expectation that someday, targeted medicine for *KRAS* can be developed. Up to now, there have been some breakthroughs with PEAC but many problems remain. Whether in case reports or clinical studies, researchers have focused mostly on disease diagnosis, staging, and

prognosis, while the clinical data related to the specific treatment of the disease were not described in detail. The current therapies for PEAC are mainly derived from those used to treat classical adenocarcinoma of the lung. Specific treatment options for PEAC have not yet been developed. Therefore, much more research on this type of carcinoma must be carried out.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-19-4171>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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