



# Hepatoid Adenocarcinoma of the Lung

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## Abstract

Hepatoid adenocarcinoma of the lung (HAL) is an comparatively rare malignant tumor originating from the lung with shorter survival. HAL morphologically and pathologically exhibits hepatocellular carcinoma (HCC)-like characteristics, while its clinical features resemble pulmonary adenocarcinoma. High concentration of alpha-fetoprotein (AFP) is often detected in the serum of HAL patients with no hepatic occupying lesion. Patients with AFP-negative HAL survive a few months longer than those with positive AFP test. HAL is a rare type of carcinoma, so there is a lack of systematic and extensive statistical research. The treatment strategy for HAL is similar to common lung adenocarcinoma. Complete surgical resection and adjuvant chemotherapy are the current major treatments for HAL patients. There are also a few of case reports suggesting that HAL patients may benefit from immunotherapy and targeted therapy. This review focuses on the clinical and pathological features, immunohistochemical staining characteristics, treatment and prognosis of HAL.

## Keywords

hepatoid adenocarcinoma of the lung (HAL), alpha-fetoprotein (AFP), histopathological characteristics, immunohistochemical staining, treatment, prognosis

## Introduction

Hepatoid adenocarcinoma (HAC) is a specific type of adenocarcinoma which is characterized by hepatoid differentiation that occurring in extrahepatic organs or tissues. In 1985, Ishikura et al.<sup>1</sup> first reported a case of HAC that was originally derived from the stomach. Relevant studies were successively published on the primary sites of HAC origin including rectum, pancreas, gallbladder, lung, kidney, adrenal gland, and uterus.<sup>2</sup> A conclusion has then been drawn that HAC most commonly originates from stomach, while pulmonary HAC is relatively rare. HAL, which is a rare subtype of HAC, shares similar histological patterns with HCC.<sup>3</sup> The histological features of these tumors involve a mixture of tubular or papillary adenocarcinoma and neoplastic cell sheets resembling HCC cells with abundant eosinophilic cytoplasm.<sup>4</sup> There are no specific immunohistochemical markers to differentiate HAC from HCC.<sup>5</sup> The clinical symptoms of HAL are not specific, and sometimes patients have cough and bloody sputum, tightness and pain in the back, cough and fever.<sup>6</sup> Although computed tomography (CT) images may provide some indications for the diagnosis for HAL, morphological and immunohistochemical evidence is still required to confirm the diagnosis.<sup>7,8</sup> Identifying the origin of HAL is crucial for its early detection and accurate treatment, which has attracted great attention.<sup>3</sup> The biological significance of HAL requires exploration. Pulmonologists should be aware of the main clinical and histopathological features of this malignant tumor to ensure diagnosis and accurate

differentiation between HAL and metastatic HCC. Due to the extremely low incidence of the disease, and diagnosis at advanced stages for the majority of patients, there are currently no specific therapies for HAL. Generally, the treatment strategy for HAL refers to those commonly used for non-small cell lung cancer (NSCLC), including surgery, chemoradiotherapy, targeted therapy and immunotherapy.<sup>9,10</sup> However, the prognosis of HAL patient remains poor.<sup>11</sup>

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## Epidemiological Characteristics

In 1981, Yasunam et al.<sup>12</sup> have reported a rare case of lung cancer with high level of serum AFP. In 1990, Ishikura et al.<sup>13</sup> defined this extremely rare tumor as pulmonary HAC for the first time. The etiology of HAL still remains uncertain. The incidence of HAL has increased significantly over the past 10 years, which may be related to an improvement in the understanding of this disease.<sup>10</sup> According to the recent reported cases, male patients with a history of tobacco use are found to predominate in all HAL cases (male: female = 2.4:1),<sup>14</sup> which is in contrast to common adenocarcinoma that mainly occurs in younger females. The age range of HAL patients were 36 and 82 years, with an average age of 60 years.<sup>15</sup> Ayub et al.<sup>11</sup> have reported that HACs follow an aggressive clinical course, and HAC patients have a median age of 65 years (range 21-88 years) and a median overall survival time of 5 months (range 1-116 months, and 95% confidence interval 3.1-6.9 months). The 1- and 3-year survival rate was only 35% and 14%, respectively. Liang ZZ et al.<sup>16</sup> included and analysed 78 patients diagnosed with HAL from SEER database from 2001 to 2016 that the median survival time was 5 months, among which stage III-IV was 4 months. Most patients tend to have a long history of smoking for over 20 years, with an average of 30 cigarettes per day.<sup>17</sup> It is well known that the main risk factors for lung cancer include smoking, chronic lung disease, environmental factors, family history and so on. HAL patients with a history of smoking tend to have a poorer prognosis than non-smokers, and so this is a risk factor of this particular type of lung cancer.<sup>1,5</sup> All above suggested that prognosis of HAL remains relatively poorer than common pulmonary carcinoma.

## Clinical Characteristics

Some HAL patients have insidious onset of symptoms. Most of them often have no specific clinical manifestations at the time of diagnosis, but may later present with cough, expectoration and bloody sputum, chest and back pain, dyspnea and weight loss.<sup>6,18</sup> HAL occurs mostly in the upper lobe, especially in the upper left lobe, partly in the lower lobe, and rarely in the middle lobe.<sup>11,19</sup> A total of 46 studies including 51 HAL patients was included in Hou Z et al. review which revealed that 52.9% of tumors were located in the upper lobe of the right lung.<sup>20</sup> The difference in HAL's predisposition may due to racial differences. The tumor usually occurs in a single nodule in a round or lobulated shape (with some burr), close to the hilum of lung or chest wall, so it can easily invade the blood vessels. Meanwhile, the pronephros and brain metastasis caused by local lymph node lesions have been occasionally reported.<sup>21</sup> Most tumors are large in size, with a maximum diameter greater than 5.0 cm and a mean diameter of 8.2 cm (range 3.5-11 cm).<sup>11</sup> In general, HAL patients have no specific clinical features, and their diagnosis is based on morphological and immunohistochemical findings rather than clinical features.

## Histopathological and Immunohistochemical Examination & Molecular Characteristic

During embryonic development, the esophagus, liver, stomach, gallbladder and lung are primitive foregut derivatives.<sup>22</sup> Due to the abnormal differentiation processes, certain tissues and organs may have a tendency to differentiate into hepatoid carcinoma.<sup>23</sup> Thus, HAC has histopathological characteristics similar to HCC, such as hepatoid cell morphology, elevated serum AFP levels, and immunoreactivity to AFP, polyclonal carcinoma embryonic antigen (CEA), and antitrypsin.<sup>21</sup> Morphologically, the HAL tumor tissue contains adenocarcinoma region, hepatoid region and undifferentiated region.<sup>9</sup> In the undifferentiated area, the tumor cells are large and homogeneous with clear boundaries and slightly eosinophilic cytoplasm. The nuclei of these cells are large, irregularly inclined to one side with a thick nuclear membranes, 1 to 3 nucleoli and coarse granular chromatin.<sup>22</sup> The majority of adenocarcinoma regions display tubular and papillary patterns. The hepatoid area presents a typical hepatocyte morphology. Tumor cells are oval or polygonal, with eosinophilic cytoplasm, large and irregular nuclei and uneven chromatin particles. Mitotic cancer cell images can be easily found.<sup>5</sup> There are many sinuses in the interstitial area, as well as in the necrotic region.<sup>24</sup> In some areas, giant multinucleated and bizarre tumor cells can also be seen. Histologically, the elevated serum AFP level is a significant characteristic related to HAL, ranging from less than 1.0 to 475,000 ng/mL.<sup>3</sup> AFP is a serum glycoprotein that exists at high levels during fetal development. It is mainly produced by mammalian embryonic liver, yolk sac and fetal digestive tube.<sup>25</sup> Thus, it may yield high specificity but poor sensitivity for AFP in the diagnosis of HCC. AFP is mainly distributed in the hepatoid differentiation area, with strong positive brownish yellow staining of the granular structure in the cytoplasm of tumor cells. The adenocarcinoma region shows positive or weakly positive staining. However, it has been found that serum AFP levels in some HAL patients are normal,<sup>11</sup> suggesting that AFP-positive cases did not represent all HAC cases. That means the diagnosis of this disease should not be ignored if AFP levels are normal. Meanwhile, Chen HF et al.<sup>26</sup> have argued that that the histologically elevated AFP levels in most HAL patients are commonly associated with poor prognosis. AFP-negative patients with HAL could survive for several months longer than AFP-positive ones. Postoperative detection of serum AFP could monitor the tendency of tumor recurrence. Luan X et al.<sup>22</sup> proposed that Hepatocyte Paraffin 1 (HepPar-1) was expressed at different levels in HAL cases. HepPar-1, a hepatocyte specific marker, is the most specific and sensitive indicator to distinguish hepatocyte differentiation. The sensitivity and specificity of HepPar-1 test in diagnosing liver cancer is 80% and 90%, respectively. It can also be used in HAL examination. Yu DZ et al.<sup>10</sup> reported that AFP was detected in 38 cases, with a positive rate of 73.7% (28/38) while HepPar-1 was detected in 29 cases, and the positive rate was 89.7% (26/29). Mao JX et al.<sup>27</sup> collated the immunohistochemical information of 94 patients

and found that the positive rates of CK19/18/8 were 92.86%, 83.33%, 82.35%, respectively. However, these biomarkers were high in HCC, reaching 75 to 95% all, making it hard to distinguish HAL from HCC.

Therefore, AFP-negative HAC should be diagnosed in combination with histomorphological examination and immunohistochemical markers (especially positive AFP and HepPar-1).

## Image Examination

The literature review reveals that chest x-ray and CT imaging are more commonly used in the diagnosis of HAL, and so far, few patients have undergone fiberoptic bronchoscopy. In general, the imaging findings of HAL are nonspecific, and none of the imaging characteristics is considered as a typical feature for direct diagnosis of HAL. Most HAL tumors primarily occur in the upper lobe, especially the adjacent pleural or mediastinal pleura, which is usually close to the chest wall or large vessels. A small part of HAL tumors appear in the lower and middle lobes.<sup>17</sup> Secondly, the tumors presented as a single nodular shadow of quasi-circular or lobulated burrs with a large diameter exceeding 5 cm. Thirdly, though none of the imaging features are considered to be the typical indicators to diagnose HAL directly, certain findings should be regarded as warnings signs of tumors. For instance, HAL tumors usually show inhomogeneous and large necrotic areas, and contrast-enhanced scan further suggests an uneven enhancement and marked areas of necrosis.<sup>18</sup> A literature review<sup>17</sup> has reported that all 5 HAL patients undergoing positron emission tomography-computed tomography (PET-CT) examination on 5 HAL patients shows high metabolic foci, and the maximum standard uptake value (SUVmax) for two patients is 5.7 and 18.6, respectively (SUV value is positively related to metabolism and common in malignant tumors). PET-CT body check can comprehensively evaluate malignant cancers that have spread into the body, assess systemic metastasis of malignant tumors, conduct early diagnosis and differential diagnosis of malignant tumors or pathological changes, perform precise tumor clinical staging, and guide or adjust the clinical treatment. Therefore, PET-CT examination can be used in the early diagnosis and clinical staging of lung adenocarcinoma liver samples. It is worth noting that the imaging diagnosis requires morphological and immunohistochemical confirmations

In summary, imaging evaluation serves limitedly but plays a useful role in selecting a therapeutic schedule for HAL, as it detects lymph node or distant metastases and helps to assess the clinical staging. Knowledge about the imaging characteristics of HAL is evolving and may indicate an association with prognosis in the future.

## Diagnosis and Staging

In 1990 Ishikura et al.<sup>1</sup> have adopted two criterion for diagnosing HAC: (a) a mixture of tubular or papillary adenocarcinoma with sheet-like or trabecular proliferation of neoplastic cells within an AFP-producing carcinoma, and (b) the presence of cells with

abundant, eosinophilic cytoplasm and centrally located nuclei in sheet-like or trabecular portions, which is similar to those of HCC cells. Haninger D et al.<sup>6</sup> proposed modification of Ishikura's diagnostic criteria for hepatoid adenocarcinoma of lung: (1) The tumor can be pure hepatoid adenocarcinoma or have components of typical acinar or papillary adenocarcinoma, signet-ring cells or neuroendocrine carcinoma and (2) AFP expression is not mandatory for diagnosis as long as other markers of hepatic differentiation are expressed. There is no specific staging method for the rare type of lung cancer which accords to 2021 WHO classification of thoracic tumors.

## Treatment

Owing to the rarity of HAL, no treatment-related clinical trials have been performed till date, and no course of treatment for HAL has been established. Only case reports and retrospective case series have been published and the therapies for HAL mainly involve NSCLC treatment regimens.

### Traditional Treatment

For early HAL disease, surgical resection is of great significance to the prognosis. Hou Z et al.<sup>20</sup> put forward a conclusion that the 2-year survival rate for patients who received surgery was 62.5%, while for patients who were unable to undergo surgery, it was only 12.5% ( $p = .009$ ). It has been reported that a patient undergoing upper right lobectomy and abdominal and mediastinal lymphadenectomy (complete resection) is pathologically diagnosed as HAC, and the tumor was classified as stage IB through postoperative pathological examination. Serum AFP level was gradually decreased but remained within the normal range after the operation. No tumor recurrence was observed 32 months postoperatively.<sup>18</sup> For the majority of patients with intermediate and advanced stages of HAL, as well as those with lymph nodes or distant metastasis, palliative lobectomy and adjuvant chemoradiotherapy are considered as appropriate treatment strategies to improve survival. Haninger et al.<sup>6</sup> have reported a 54-year-old white female smoker who was diagnosed with stage IV HAL with rib metastasis. The patient received neoadjuvant chemotherapy, surgery and adjuvant chemotherapy and radiotherapy and was still alive 9 years after the symptoms presentation. This is the longest survival of any HAL patient by far. Muroyama<sup>28</sup> reported that a patient underwent NSCLC chemotherapy regimens as the first and second line, but had clinical progression. After third-line oral S-1 administration, the serum AFP level significantly dropped and the patient survived more than 19 months after disease presentation. Motooka Y et al.<sup>29</sup> used cisplatin and gemcitabine as adjuvant chemotherapy in a patient with IB stage HAL who survived 51 months without tumor recurrence. Papatsimpas G et al.<sup>30</sup> reported a case of chest CT showing segmented soft tissue masses extending from the tip of the left lung to the middle and posterior mediastinum with no lymph nodes metastasis, which was confirmed to be a stage IIIA pulmonary HAC. After diagnosis, the patient

received concurrent 60Gy/2Gy/30F radiotherapy and intensity modulated radiotherapy using 6-MVX rays, accompanied by two cycles of paclitaxel plus cisplatin therapy. At the same time, CT examination and re-examination of serum AFP levels showed that the patient's lung lesions improved and serum AFP levels decreased after four cycles. Wang WT et al.<sup>31</sup> reported a HAL patient who received radiation therapy alone. After 50Gy/25 fractions of radiotherapy, the tumor shrank significantly while the patient refused to accept further treatment after the radiotherapy of 60Gy/30f. The ultimate survival benefit from radiotherapy was 12 months. In conclusion, HAL patients can benefit from conventional surgery and chemoradiotherapy.

### Targeted Therapy

In recent years, with the remarkable development of gene molecular technology, targeted therapy and immunotherapy have become the popular treatment methods for tumor therapy. Tyrosine kinase inhibitors (TKIs) achieve remarkable therapeutic efficacy against epidermal growth factor receptor (EGFR)-mutated tumors.<sup>32</sup> Combined treatment of adjuvant chemotherapy and TKI can prolong the survival time of patients who are intolerant to surgery to some extent. However, the molecular markers of targeted therapeutic significance, such as EGFR mutations, are frequently absent in distinguishing HAC from common pulmonary carcinoma, in which the EGFR mutations are present in 30% to 60% of Asian patients.<sup>26</sup> A few patients with HAL who have been genetically tested positive for EGFR, kirsten rat sarcoma viral oncogene (KRAS), tumor suppressor homolog 1 (FAT1), and tumor protein 53 (p53) were considered to be more rare in this disease that is already rare. There are only some case reports. Recently, Gavranic et al.<sup>33</sup> have reported the novel use of sorafenib in combination with platinum-based doublet chemotherapy in patients with EGFR wild-type HAL, which leads to overall stable disease and achieved the longest survival time for unresectable stage IV HAL patients. Chen HF et al.<sup>26</sup> have adopted a therapeutic regimen combining adjuvant chemotherapy with pemetrexed and cisplatin and targeted therapy of icotinib on a HAL patient. Subsequently, the patient received osimertinib and anlotinib due to EGFR exon 20 T790 M mutation, attaining a progression-free survival for months, and the disease remained stable and the patient was still alive. Therefore, platinum-based chemotherapy combined with targeted therapy may be a beneficial therapy for HAL. To sum up, targeted therapy of HAL lacks abundant research and more experimental data.

### Immunotherapy

Clinically, the immunotherapeutic biomarkers mainly include programmed death receptor-1 (PD-L1), microsatellite instability (MSI), and tumor mutation burden (TMB). The PD-L1 expression is a logical biomarker used for predicting the response to anti-PD1/PD-L1 immunotherapies, tumors with

MSI-high are exquisitely sensitive to PD-L1 inhibitors, and high TMB predicts a better response to immunotherapies. Based on the latest literature review composed by Chen LL et al.<sup>2</sup> a 65-year-old female patient obtained an overall survival of 52 months treated with multiple lines of chemotherapies and PD-1 inhibitor, sintilimab. Basse V et al.<sup>34</sup> reported a clinical trial treatment for PD-L1 negative patients without EGFR, KRAS, ALK or ROS1 molecular alterations to evaluate the efficacy of durvalumab as an anti-PD-L1 therapy. The results showed that the patients finally obtained a partial response following immunotherapy. They attributed the efficacy of immunotherapy to the underlying mismatch repair (MMR) deficiency status. This is specifically seen in young patients lacking indicated therapies or immunotherapies according to the current guidelines, and this requires further investigation. The above literature shows that immunotherapy maybe beneficial to HAL patients. For patients who are positive or negative for PD-L1 or PD-1. Immune blockers may be used experimentally when no drug options are available.

To sum up, surgery is the best option for early stage HAL patients, and platinum-based chemotherapy with radiotherapy is frequently used as an effective clinical treatment strategy. Targeted therapy and immunotherapy have played an instrumental role in the treatment of HAL and have been gradually recognized clinically in recent years. Platinum-based chemotherapy and targeted therapy have evolved as new treatment strategies for HAL. However, there is still no effective gene therapy for HAL patients, which needs to be further studied in the future. Otherwise, immune checkpoint inhibitors (ICIs) including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), PD-1 or PD-L1 may join the therapeutic armory of HAL in the future.

### Prognosis

The prognosis of HAL patients still remains to be poor because the patients have hidden clinical features with no special imaging manifestations, leading to the late stage diagnosis of the disease. HAL tumor are extremely invasive and easily metastasizes to the brain, liver, adrenal gland, gingiva, vertebral body, pancreas and pericardium,<sup>7,17,35-37</sup> so the best treatment opportunity has already been lost. Therefore, the prognosis in HAL patients is generally worse than that in NSCLC patients<sup>16</sup> and the most important prognostic factor is the disease stage at the time of diagnosis.<sup>38</sup> The reported treatment modalities and outcomes of HAL are shown in **Table 1**.<sup>2,6,11,15,18,26,29,33,35,36,39-42</sup> For gastric HAC, Nagai et al.<sup>43</sup> have reported that whether AFP is expressed or not, the prognosis of gastric HAC is worse than that of ordinary gastric cancer, while the prognosis of AFP-positive gastric cancer without hepatocellular structure is similar to that of ordinary gastric cancer. That is to say, the prognosis of gastric HAC is based on morphological characteristics rather than serum AFP levels. But Chen HF et al.<sup>26</sup> argued that most HAL patients had increased serum AFP levels in histopathologic analysis, showing association with poor prognosis.

**Table 1.** The reported treatment modalities and outcomes of HAL

Ref.	Sex	Age (year)	Smoking Status	Stage	AFP (ng/ml)	Ki-67 (%)	VEGF expression	Molecular characteristics	Treatment	Outcome	OS (months)
[6]	M	51	Yes	IIIB	1.3	NT	NT	NT	Surgery, CRT	Died	14
	M	52	Yes	IV	NT	NT	NT	NT	Surgery, CRT	Died	37
	M	64	Yes	IV	1.0	NT	NT	EGFR mutation negative	Surgery, CRT	Died	10
	M	54	Yes	IV	NT	NT	NT	NT	CRT	Died	108
	M	60	Yes	IV	4410	NT	NT	NT	CRT	Died	1
[11]	M	61	Yes	IA	Negative	NT	NT	NT	Surgery, RT	Died	6
[15]	M	47	Yes	IV	Negative	NT	NT	EGFR mutation and ALK rearrangement were negative	Surgery	Died	4
[18]	M	59	Yes	IB	Negative	20	NT	NT	Surgery	SD	23
[26]	M	53	No	NT	3296	20	NT	EGFR mutation positive	Surgery, CRT (pemetrexed, cisplatin), TT (icotinib, osimertinib)	SD	29
[29]	M	69	NT	IB	4497	NT	NT	EGFR mutation negative	Surgery, CT (cisplatin, gemcitabine)	SD	51
[33]	M	64	NT	IV	181	NT	NT	EGFR mutation negative	CRT (carboplatin, paclitaxel), TT (sorafenib)	Died	11
[34]	F	65	No	IV	6818	NT	Positive	KRAS mutation positive, ALK and EGFR mutation negative	CT (docetaxel, oxaliplatin, pemetrexed, gemcitabine, nedaplatin), TT (bevacizumab, anlotinib), IT (sintilimab)	Died	52
[35]	M	43	Yes	NT	NT	NT	NT	EGFR mutation, KRAS mutation, ALK rearrangement, ROS1 alteration were negative	IT (durvalumab), CRT (carboplatin, docetaxel)	NT	NT
[36]	M	70	Yes	IV	Negative	NT	NT	TP53 mutation positive	CRT (docetaxel, nedaplatin), TT (erlotinib, bevacizumab, anlotinib)	Died	9
[39]	M	70	Yes	IIIA	Negative	NT	NT	NT	Surgery	Died	18
[40]	F	62	Yes	IIIA	9010	NT	NT	EGFR mutation, BRAF 600E mutation, ALK rearrangement and ROS1 fusion were negative	Surgery, CRT, IT (nivolumab)	Died	14
[41]	M	61	NT	IIIA	Negative	NT	NT	NT	CRT (pemetrexed, cisplatin)	Died	55
[42]	M	54	NT	IV	Negative	NT	NT	EGFR mutation, KRAS mutation, ALK rearrangement were negative	CRT	Died	3
[43]	M	79	Yes	NT	698	NT	NT	NT	TT (erlotinib)	Died	.83

(continued)

Table 1. (continued)

Ref.	Sex	Age (year)	Smoking Status	Stage	AFP (ng/ml)	Ki-67 (%)	VEGF expression	Molecular characteristics	Treatment	Outcome	OS (months)
[49]	M	71	No	IIIC	79 480	80	NT	FAT 1 alternation positive	Interventional therapy, RT, TT (anlotinib)	Died	1

M, male; F, female; CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; TT, targeted therapy; IT, immunotherapy; NT, not noted; SD, stable disease; OS, overall survival

Additionally, AFP-negative HAL patients could survive several months longer than AFP-positive ones. For instance, a AFP-negative woman with stage IV HAL had the longest survival of 9 years in all cases, and her metastatic disease was completely under control by chemoradiotherapy.<sup>6</sup> Papatsimpas et al.<sup>30</sup> have also suggested that patients with normal serum AFP levels tend to have better overall survival after tumor relapse. They argued that the condition of metastatic tumor and the concentration of serum AFP were significant for monitoring therapeutic efficacy and prognosis in HAL patients. Therefore, the prognosis of HAL patients mainly depends on cellular differentiation, whereas morphology or serum AFP levels need to be carefully considered. Koide et al.<sup>44,45</sup> have considered that a higher Ki67 index in gastric HAC may denote a worse prognosis than common gastric carcinoma, so it is more possible that a higher Ki67 index in gastric HAC patients may influence the prognosis. Whether this conclusion can also be applied to HAL or not needs further verification. Vascular endothelial growth factor (VEGF) can stimulate the growth of endothelial cells, and its expression can act as a risk factor in the prognosis of lung cancer.<sup>46</sup> Scholars have shown<sup>8</sup> that VEGF is highly expressed in several HAL patients, and most of them are diagnosed as an advanced stage with vascular invasion. Further studies found that the incidence of vascular invasion was 20% in stage I HAL patients.<sup>47,48</sup> Therefore, the expression of VEGF is also one of the factors affecting the prognosis of HAL. Mao JX et al.<sup>27</sup> analyzed that the majority of female patients were diagnosed at an advanced stage (stage III or IV), their prognosis seemed better. Estrogen protection may contribute to the better prognosis in women, but the exact mechanism is still unknown.

Generally, the prognosis of HAL patients remains worse compared to common pulmonary carcinoma, with a shorter overall survival time and a greater possibility of metastasis to other organs. The earlier diagnosis may lead to a better prognosis. Furthermore, the morphological characteristics, serum AFP levels, Ki-67 index and VEGF expression are all relevant factors for the prognosis of HAL cases. As for other prognostic factors, more cases and more investigations are warranted.

## Conclusion

HAL is morphologically similar to the appearance of HCC, excluding the lung metastasis caused by HCC. HAL is predominant in middle-aged men with a history of smoking, and

without any liver disease or family history. As a rare type of carcinoma, there is a lack of sufficient sample data and systematic and extensive statistical research worldwide, so the disease is relatively difficult to diagnose and treat. Based on previous cases, HAL can be diagnosed early and the survival rate can be improved only by enhancing comprehensive knowledge on HAL. It is necessary to explore the typical features and histological characteristics including increased AFP levels. Because of low incidence rate and limited case information, a standard treatment regimen is lacking, and surgery, radiotherapy and chemotherapy remain the main treatment options for HAL. This suggests that early and localized tumors should undergo surgical resection, while advanced HAL patients are usually treated with platinum-based chemotherapy and radiotherapy. Some patients harboring EGFR, KRAS mutations or ALK rearrangement may undergo targeted therapy and immunotherapy. Till now, there is no effective therapeutic drug for HAL caused by gene anomalies, which requires continued research in the future.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


## Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

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