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Research article

Pathological analysis of hesperetin-derived small cell lung cancer by artificial intelligence technology under fiberoptic bronchoscopy

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Abstract: Lung cancer is one of the most common tumors. There are 1.8 million new cases worldwide each year, accounting for about 13% of all new tumors. Lung cancer is the most important cause of cancer-related deaths. 1.4 million people die of lung cancer each year. This article uses artificial intelligence technology to analyze the pathology of hesperetin-derived small cell lung cancer under fiberoptic bronchoscopy. This article takes 48 lung slice samples as the research object. Among them, 36 cases of lung small cell carcinoma have history slices from Lhasa City Institute of Biology, the patient has complete cases, and the other 12 normal lung slices come from Xinjiang Biotechnology Laboratory. In this paper, the above-mentioned 36 lung cancer slices became the study group, and 12 normal slices became the reference group. This article presents a method for hesperetin-fiber bronchoscope to study the pathological mechanism of lung small cell carcinoma (H-FBS), which is used to study slices. The above-mentioned 48 samples were taken for slice observation. First, the 48 slices were technically tested by artificial intelligence fiber bronchoscope combined with hesperetin derivatives, and then the slice observation results were verified by CTC technology. In addition, in each step, the C5orf34 in the tissue is detected separately, which is beneficial to adjust the content of C5orf34 so that the treatment of lung cancer can control the development of lung cancer under fiberoptic bronchoscopy. Experimental results show that the diagnostic accuracy rate of this method is 97.9%, which is higher than that of lung biopsy (89%); compared with multiple CTC detection, the cost is low and the time is shor.

Keywords: hesperetin derivatives; lung small cell carcinoma; circulating cell detection technology; fiberoptic bronchoscopy

1. Introduction

The pathology of small cell carcinoma of the lung (SCLC) is very complicated, which also causes difficulties in treatment. There are many problems in traditional detection, because there is no strict control in the detection process, and many people are directly detected as cancer. There are many factors affecting the prognosis of non-small cell lung cancer SCLC and the mechanism is more complicated. Although comprehensive tumor treatment has improved the prognosis of patients, it is still not satisfactory. Many studies are based on new immunotherapies, generally by setting pathological thresholds to further study abnormal samples.

When Arrieta explored the mechanism of IL-27 + CD4 + T cells entering the pleural space, it was found that IL-27 can activate the STAT3 signaling pathway [1]. Dómine reviewed the diagnostic performance of ADA in SCLC, and the results showed that the commonly used 40IU/L SCLC threshold has a lower negative likelihood ratio, which may be more helpful to rule out the diagnosis of SCLC [2]. On the contrary, the study of TRIGO showed that when the SCLC threshold is higher than 65IU/L, the positive likelihood is higher, and the positive predictive value of the prevalence of SCLC is higher. Such a threshold may be more helpful for confirmation and exclude the diagnosis of TP poor efficiency [3]. Morrison enrolled 11 patients with SCLC who received immunotherapy. The expression of H-FBS in the peripheral blood was detected before treatment, 3 to 5 cycles after treatment and when the disease progressed. The results showed that all patients who responded to immunotherapy, the number of PD-L1 positive CTCs decreased or remained unchanged, while the number of PD-L1 positive CTCs in all patients with disease progression increased and the expression of PD-L1 could be detected on all CTCs [4]. Donnenberg proposed that the dynamic increase in the number of PD-L1 positive CTCs can be an effective marker for predicting the resistance of SCLC patients to immunotherapy [5].

Gehling observed similar results. He found that after 6 months of immunotherapy, all patients with H-FBS expression in the peripheral blood had disease progression, while those with no H-FBS expression were affected by immunotherapy [6]. Neagu first detected the expression of PD-L1 on the peripheral blood CTC of patients with metastatic breast cancer, which confirmed the expression of PD-L1 protein on the CTC cell membrane and verified the feasibility of H-FBS detection [7]. The results of Burgos-Ojeda D showed that radiotherapy can induce an increase in the expression of H-FBS, but no association between H-FBS and prognosis was found [8]. Ali also observed an increase in H-FBS expression in patients receiving radiotherapy or concurrent chemo radiation, and found that patients with positive baseline H-FBS had a poor prognosis. For patients receiving chemotherapy, studies have detected the expression of H-FBS before and after chemotherapy and found that the detection rate has increased. H-FBS is considered to be an independent predictor of poor prognosis of chemotherapy [9]. In patients with stage Ia lung adenocarcinoma, Boldrini selected 4 acinar lung adenocarcinomas with good prognosis and 4 solid lung adenocarcinomas with poor prognosis for microarray analysis of gene expression profiles, and screened out C5orf34 as an up-regulation difference of the genes [10]. The above research results collectively suggest that the dynamic change of H-FBS expression can be an effective marker for evaluating treatment response during immunotherapy. In addition, detection and treatment are isolated. In the actual treatment process, it is impossible to make timely pathological responses to the new cell state. Although the

viewpoints and methods put forward by these scholars are quite accurate, there are still some small problems in the research process.

In this paper, hesperetin-fiber bronchoscope is used to study the pathological mechanism of lung small cell carcinoma (H-FBS), and this method is used to study the slices. The samples were sliced for observation. First, the slices were technically tested by artificial intelligence fiber bronchoscope combined with hesperetin derivatives, and then the slice observation results were verified by CTC technology. In addition, in each step, the C5orf34 in the tissue is detected separately, which is beneficial to adjust the content of C5orf34 so that the treatment of lung cancer can control the development of lung cancer under fiberoptic bronchoscopy.

2. Small cell lung cancer and fiberoptic bronchoscopy

2.1. Pathogenesis and treatment of small cell lung cancer

Changes in C-MET in small cell lung cancer (SCLC) include point mutations, amplification, fusion, and protein overexpression, which are associated with poor prognosis [11]. In SCLC patients, METexon14 jump mutations account for about 3–4%, and the prevalence of MET amplification is 1–5%. Past preclinical and clinical studies have shown that in other genome subgroups, MET activation is not only a primary oncogenic driver mutation, but also a secondary driver of acquired targeted therapy resistance [12]. Therefore, drugs targeting c-MET are a promising strategy for the treatment of non-small cell lung cancer [13]. At present, many drugs targeting MET (small molecule TKI, MET antibody, HGF antibody) have undergone clinical research [14]. Human epidermal growth factor receptor 2 (HER2) is mainly highly expressed in breast cancer. In recent years, it has been found that about 1–2% of SCLC patients also have HER2 activating mutations. The three main mechanisms of HER2 changes are: HER2 protein overexpression, HER2 gene amplification and HER2 gene mutation. The result of overexpression of Her2 is that the protein expressed by the gene increases, and the proteins it expresses are transported to the outside of the cell, so it is easy for Herceptin to be discovered and killed by the drug, and Her2 gene amplification refers to the enrichment of her2 genes. The amount of DNA is increased in the cell, but it may not be able to express the protein, and thus cannot be recognized by the drug [15].

1) Abnormal C5orf34 causes lung cancer

C5orf34 is a protein encoded by the C5orf34 gene. C5orf34 is conserved in mammals, birds and reptiles [16]. The C5orf34 protein contains two mammalian conserved domains: DUF4520 and DUF4524. C5orf34 consists of 638 amino acids and has a molecular weight of 72.7 kDa [17]. According to the human protein profile, C5orf34 is most abundantly expressed in stomach, small intestine, testis, skeletal muscle and myocardium in humans, and is low in normal lung tissue [18]. At present, the exact function of C5orf34 in humans is still unknown. There are reports in the literature that the C5orf34 gene may be related to gestational diabetes [19]. According to the protein structure, it is speculated that it may be related to kinase-related cell functions, and may involve gene regulation and cell proliferation [20]. This suggests that C5orf34 may be expressed differently among different subtypes of lung adenocarcinoma, thereby affecting the prognosis [21]. The above are just big data speculations, and did not really verify the gene function of C5orf34 [22]. Studies have confirmed that interference with C5orf34 gene can reduce the proliferation, invasion and migration of human lung adenocarcinoma cells A549 and SPC-A1 [23]. But only about 20% of SCLC patients

will respond to immune checkpoint inhibitors. Taking into account the possible adverse reactions and economic burdens in immunotherapy, it is of great clinical significance to find biomarkers that can accurately predict the response of immunotherapy. This is also the biggest problem facing SCLC immunotherapy at this stage [24]. Detection of PD-L1 expression in tumor tissues by immunohistochemistry (IHC) can predict the tumor's response to immunotherapy to a certain extent, but it is not a perfect predictive marker [25]. C5orf34 was significantly positively correlated with T and pathological stage ($P < 0.05$), which was basically consistent with the clinical analysis results in the TCGA database. In addition, the positive rate of C5orf34 (22.2% and 31.9%) in lung squamous cell carcinoma and adenocarcinoma is not statistically significant, which suggests that the expression of C5orf34 may not be related to the pathological type of SCLC. The prognostic analysis results of this study found that C5orf34 does not affect the prognosis of stage I patients. However, for patients with stage II to III, C5orf34 positive DFS was significantly lower than that of negative patients. This phenomenon was consistent in the subgroup analysis of T stage and G2~3. This suggests that C5orf34 may be closely related to the development and differentiation of tumors. The above clinical analysis results are consistent with the phenotypic results of the gene cell function.

2) Difficulties in the treatment of lung cancer

Therefore, a tissue biopsy at a single site cannot well represent the overall tumor status of the patient. During the course of the disease, the expression of PD-L1 in tumor tissues at different time nodes is not fixed, but is dynamic and has temporal heterogeneity. PD-L1IHC currently lacks standardized testing standards and testing procedures, and different immunotherapy drugs support different PD-L1 testing methods. The antibodies used in different detection methods and the definition of PD-L1 positive are different, which brings difficulties to clinical applications. Although multi-site or continuous biopsy can partially solve the above problems, it is generally considered not feasible due to the invasive nature of biopsy and potential risks such as tumor metastasis. Therefore, there is an urgent need for new detection methods in the clinic to accurately predict the efficacy of immunotherapy, and to dynamically monitor the expression of PD-L1 for a long time to better reveal the biological characteristics of the tumor and monitor the treatment response. It is expected to reveal key issues such as how SCLC evolves and develops drug resistance after receiving immunotherapy. At present, the "seed-soil" theory of tumor metastasis is generally accepted. As a precursor of metastasis-driven, CTC retains the characteristics of primary tumor cells and metastatic tumor cells. Therefore, the expression detection of H-FBS can more comprehensively reflect the important biological characteristics of primary tumors and metastases, and can provide important supplementary information about drug sensitivity, treatment efficacy prediction and prognosis judgment. This article summarizes the current research on the expression of H-FBS in the field of SCLC immunotherapy, assesses the potential role of H-FBS expression in predicting the efficacy of immunotherapy and the application of dynamic changes in the assessment of treatment response, and explores the limitations of H-FBS detection and application prospects.

2.2. CTC in SCLC immunotherapy

As the “precursor seeds” of tumor metastasis, CTCs are expected to be used as markers for tumor diagnosis and treatment monitoring. To achieve this goal, the development of real-time and accurate analysis techniques for monitoring the dynamic changes of CTCs in the body is essential. CTCs in vivo detection technology is based on the fast-flowing blood in the circulatory system of the

body, even lymph, cerebrospinal fluid and other body fluids. It can record the dynamic changes in the number of CTCs in different parts of the body in real time under real physiological conditions, recruit and capture tumor cells. At present, the main animal models used in the in vivo detection of CTCs are mouse tumor models, including intravenous tumors, subcutaneous tumors, and orthotopic tumors. There are two main methods for quantitative analysis of CTCs in vivo. One is based on optical IVFCs to automatically record the fluorescent signals and photoacoustic signals produced by target cells to count CTCs.

The other is to capture CTCs first, and then stain the tumor cells, observe under a microscope, and count the number of cells. The NE-imFISH platform can detect CTC in different cancers, and has high sensitivity and specificity, which is of great significance for improving the clinical management of cancer patients. Due to the limited size of blood vessels in the body, blood in the body can also be drained outside the body, combined with efficient in vitro enrichment methods to capture CTCs. However, CTCs detection focuses on the dynamic changes of the number of CTCs with the development of tumor development. Therefore, it is required to develop a technology that can separate high-quality CTCs with integrity, high vitality, and high purity. To this end, the developed CTCs in vitro detection technology has added the function of mild and specific release of captured CTCs; a negative selection method that specifically enriches and removes normal blood cells is constructed to obtain CTCs; integration can directly culture the enriched CTCs in situ, modules for analysis, etc. The in vivo capture technology of CTCs that has been developed can effectively guarantee the quality of CTCs before and during the capture process, but downstream analysis of them after in vitro also faces problems such as cell inactivation and distortion, and new functions need to be integrated into the capture device. It is convenient for CTCs to be released from the surface of the captured matrix in the body, thereby meeting the requirements of subsequent CTCs culture and molecular analysis. In addition, it is also possible to develop an integrated diagnosis and treatment CTCs detection system to capture and kill tumor cells in the body, or recruit metastatic tumor cells, reduce tumor burden, and benefit therapeutic interventions, such as stent implant-based CTCs in vivo recruitment technology.

A number of studies have shown that the successful isolation and identification of CTC can further detect the expression of H-FBS in SCLC patients receiving chemotherapy and targeted therapy, so as to explore its value and significance in the clinical practice of SCLC immunotherapy. SCLC single-agent treatment of rabbit disease is not effective. The current research focus is on combination therapy. IMpower 133 study applies atilizumab combined chemotherapy to ES-SCLC-line treatment. Immunotherapy has completely changed the treatment pattern of SCLC and has become the new standard of third-line and first-line treatment. At the same time, it has also opened up the exploration of finding suitable people, ideal treatment opportunities and best treatment strategies. However, in the field of immunotherapy, whether CTC can effectively predict the efficacy and evaluate the prognosis remains to be further explored. A study examined the peripheral blood CTC levels in 96 patients with metastatic SCLC who had progressed after chemotherapy and were ready to receive Nivolumab. The analysis found that patients with high CTC levels at baseline had a poor prognosis, while those with PFS over 6 months had a poor prognosis. The 24 patients with disease progression showed that the average value of CTC was significantly higher than that before the start of immunotherapy (52.5/7.5 mL *vs.* 30/7.5 mL, P = 0.03). Therefore, the increase of CTC content indicates immunotherapy. The effect is not good, which was also confirmed in another similar study. A meta-analysis of 2883 patients included in 22 studies reported that the sensitivity of

IFN-γ to diagnose SCLC was 89% and the specificity was 97%. Similarly, due to its high detection cost and lack of corresponding accurate clinical diagnosis thresholds, its clinical application is also limited. So far, three meta-analyses have reported the diagnostic significance of IL-27 for SCLC. The most representative study included 1157 PE patients. The results showed that the diagnostic threshold of IL-27 for SCLC was 591.4ng. The sensitivity and specificity of L are 93.8% and 91.7%, respectively, so its diagnostic efficacy is worthy of recognition and can be used as a biomarker for the diagnosis of SCLC. However, the cost of detecting IL-27 in PE is relatively high, and it lacks the recognized best diagnostic threshold. Therefore, the blood flow rate and flow can be estimated through this time width, namely:

$$SCLC = \frac{n\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}(x_i - \overline{x})(xj - \overline{x})}{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}(xi - \overline{x})^2} = \frac{n\sum_{i=1}^{n}\sum_{i\neq j}^{n} w_{ij}(x_i - \overline{x})(xj - \overline{x})}{S^2\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}} \tag{1}$$

At present, CTC is considered to be an independent predictor of the poor effect of SCLC immunotherapy. The decrease of CTC content during immunotherapy indicates that the patient will benefit from immunotherapy, while the increase of CTC content indicates the poor prognosis of the patient. Application of 3H-FBS expression detection in SCLC immunotherapy Previous studies have explored the value and role of H-FBS detection in traditional treatments such as surgery, radiotherapy and chemotherapy. This is useful for a better understanding of the interaction between H-FBS and immunotherapy. The role relationship is of great significance. In addition, because the pulmonary vein is closer to the primary tumor than the peripheral vein, the number of CTCs in the pulmonary vein is relatively concentrated, so drawing blood from the pulmonary vein can increase the detection rate of H-FBS. Dong is equivalent to taking 114 early SCLC patients' pulmonary venous blood to detect the expression of H-FBS. It is found that patients with positive H-FBS have shorter postoperative disease-free survival (DFS) and relapse earlier after surgery. Based on the above studies, H-FBS is currently considered to be related to the poor prognosis of SCLC. It interacts with the immune system to form an immunosuppressive tumor microenvironment, which enables tumors to escape the clearance of the immune system, and has a stronger ability to invade and metastasize. The prognosis of the patient is poor. In addition, traditional treatments such as radiotherapy and chemotherapy can induce the up-regulation of the expression of H-FBS. Radiotherapy and chemotherapy combined with immunotherapy may have a sensitization effect, so that more patients can benefit from immunotherapy. Therefore, further exploration of the interaction between H-FBS and immunotherapy has important value and significance for the clinical practice of immunotherapy.

2.3. Fiberoptic bronchoscopy technique

With the development of immunotherapy in SCLC, more and more patients have the opportunity to benefit from immunotherapy. It is worth noting that many patients begin to use immunotherapy after receiving chemotherapy, radiotherapy and targeted therapy. Therefore, the influence of previous treatment on the detection results should be fully considered when evaluating the expression of H-FBS. Fiberoptic bronchoscopy can be observed directly. This technology can

detect lung cancer early, and can also improve the detection rate of carcinoma in situ through lung imaging fluorescence endoscopy. And the operation is convenient, safe, and the patient's pain is small. It can be used as the pre detection of cancer.

After EGFR-TKI resistance in advanced SCLC patients, fiberoptic bronchoscopy is the first choice to detect the driving gene. Among them, surgical resection is undoubtedly the gold standard, but for patients with poor physical condition or late staging, surgical resection and re biopsy is often not feasible. Percutaneous needle aspiration biopsy is a simple and relatively safe method for histological diagnosis and genotyping of primary/metastatic parenchymal lesions located at or near the body surface. It has higher accuracy under the guidance of imaging technology (including CT, ultrasound, etc.)

$$SCLC = \frac{\sum_{j=1}^{k}\sum_{h=1}^{k}\sum_{t=1}^{n_j}\sum_{r=1}^{n_h}\left|y_{ij}-y_{hr}\right|}{2n^2u} \tag{2}$$

In order to improve the sensitivity of electrochemical detection, the cyclic DNA complex can be immobilized on the electrode for rolling loop amplification

$$u_h \le u_j \le \ldots \le u_k \tag{3}$$

$$G = G_w + G_{nb} + G_t \tag{4}$$

$$P(d_i, w_j) = P(d_i)P(w_j|d_i); P(w_j|d_i) = \sum_{k=1}^{K} P(w_j|z_k)P(z_k|d_i) \tag{5}$$

But it cannot collect enough tumor cells for multiple mutation analysis, and the risk of complications (including bleeding, pneumothorax, pleural dissemination, etc.) is relatively high. The antibody horseradish peroxidase conjugated gold nanoparticles were used as signal probes to trigger enzyme catalyzed reaction when the cancer cells were captured, resulting in amplified current response

$$G_{jh} = \frac{\sum_{Z=1}^{h_j}\sum_{r=1}^{n_h}\left|y_{ji}-y_{hr}\right|}{n_j n_h (u_j + u_h)} \tag{6}$$

$$l_{ssim} = 1 - \frac{(2\mu_x\mu_y + C_1)(2\sigma_{xy} + C_2)}{(\mu_x^2 + \mu_y^2 + C_1)(\sigma_x^2 + \sigma_y^2 + C_2)} \tag{7}$$

$$G_t = \sum_{j=2}^{k}\sum_{h=1}^{j-1} G_{jh}(p_j s_h + p_h s_j) D_{jh}(1 - D_{jh}) \tag{8}$$

Compared with percutaneous biopsy, transbronchial lung biopsy can obtain more tumor cells, and the risk is relatively low. Formalin fixed paraffin embedded specimens of traditional bronchoscopy are widely used in clinic because of its convenience, long storage time and low cost. The technique of obtaining lesion specimens of lung parenchyma by percutaneous puncture for

cytology, histology and microbiology examination. Mostly operate under B-ultrasound, X-ray fluoroscopy or CT positioning. Therefore, in many cases, two different aptamers are coupled to the surface of glassy carbon electrode at the same time

$$\wp_{\kappa} = \frac{2k}{k+1} + [\frac{1}{2} + \frac{1}{2k}][\frac{c_2 - c_1}{3}]^2 + \frac{2(c_2 - c_1)}{3} \tag{9}$$

$$d_{jh} = \int_0^{\infty} dF_j(y) \int_0^{y} (y - x) dF_h(x) \tag{10}$$

$$\ln \mathrm{gdp}_{\mathrm{it}} = a_0 + a_1 du * dt + \sum_{i=1}^{N} b_j Xu + \varepsilon_u \tag{11}$$

Compared with the single aptamer modification strategy, the sensitivity of the double aptamer modified part is improved. In addition, the sandwich biosensor can also increase the detection sensitivity through signal amplification technology

$$f(x) = \frac{1}{Nh} \sum_{i=1}^{N} k(\frac{X_i - x}{h}) \tag{12}$$

$$k(x) = \frac{1}{\sqrt{2\pi}} \exp(-\frac{x^2}{2}) \tag{13}$$

$$h_t = \tanh(w_c x_t + u_c(r_t \Theta h_{t-1}) + b_c) \tag{14}$$

$$h_t = z_t \Theta h_{t-1} + (1 - z_t) \Theta h_t \tag{15}$$

Using LiFePO4 as a signal probe can not only expand the application of lithium-ion battery materials, but also expand the application of biosensors.

$$\sigma t = \frac{\sqrt{\frac{1}{n} \sum_{i=1}^{n} (FI_{it} - FI_{it})^2}}{FI_{it}} \tag{16}$$

$$u_{(j|i)} = w_{ij} A_i \tag{17}$$

$$x_{\mathrm{H}} = \frac{p_2 - p_1 + 1}{2} \tag{18}$$

The principle of this method is to use platinum nanoparticles as catalytic probe and tyramine functionalized coordination polymer as electroactive signal label. ICPs can be deposited on the target cell membrane layer by layer under the catalysis of Pt, and form bio conjugates on the electrode

through sandwich reaction. In the presence of CTC, the following relationships exist

$$\ln(\frac{FI_{it}}{FI_{it}-1})=\alpha+\beta\ln FI_{it}-1+v_i+\Im_t \tag{19}$$

$$\psi=\sum_{x=1}^{\theta}Vx=\sum_{x=1}^{\vartheta}(\frac{Wx}{\sum_{1}^{n}W_{\Im}}Sx) \tag{20}$$

Thus, the peak current of ICPs increases obviously. According to the change of current, the number of CTC can be detected by differential pulse voltammetry (DPV). Biosensor is an instrument that is sensitive to biological substances and converts its concentration into electrical signals for detection. The sandwich biosensor greatly improves the sensitivity and detection efficiency.

$$r=\frac{\alpha}{1-\beta} \tag{21}$$

$$\theta=-\frac{1}{T}\ln(1+\beta) \tag{22}$$

$$\theta(p,q)=\arctan\left(\frac{L(p,q+1)-L(p,q-1)}{L(p+1,q)-L(p-1,q)}\right) \tag{23}$$

Then, after capturing CTC with EpCAM modified magnetic nanospheres, MUC1 aptamer was attached to the cell surface to form a sandwich structure

$$\ln(\frac{FI_{it}}{FI_{it}-1})=\alpha+\beta\ln FI_{it}-1+\varphi X_{it}-1+v_i+\tau_t \tag{24}$$

$$k_{t1}[i]=\sum_{j}\cos(w_i^1,w_j^2) \tag{25}$$

3. Pathological research design of artificial intelligence fiberoptic bronchoscopy combined with hesperidin derivatives

3.1. Objects

Twelve lung cancer sections and 12 normal sections were extracted from Lhasa Institute of biology and Xinjiang Institute. In this paper, the method of hesperidin fiberoptic bronchoscopy (H-FBS) was proposed to study the pathological mechanism of small cell lung cancer.

3.2. Steps

The above 48 samples were observed in sections. Firstly, the 48 sections were detected by artificial intelligence Fiberoptic Bronchoscopy Combined with hesperidin derivatives, and then the results were verified by CTC technology. In addition, the detection of C5orf34 in each step is helpful to regulate the content of C5orf34, so that the treatment of lung cancer can control the development of lung cancer under fiberoptic bronchoscopy.

Due to the invasive operation, patient tolerance and tumor heterogeneity of artificial intelligence fiberoptic bronchoscopy, it is sometimes difficult to achieve or fail to achieve the expected results. Although liquid biopsy including peripheral blood is simple and feasible, there are mainly the following risks. The first risk is bleeding, which is the most troublesome clinical complication, because during the bronchoscopy process, it may cause lesions or vascular bleeding. The second risk is that it is easy to stimulate the heart to induce cardiovascular and cerebrovascular diseases, or cause Respiratory failure, etc. The purpose of this study is to explore the possible correlation between the mutation status of small lung cells and the clinical factors of patients, as well as the follow-up treatment. We hope to predict the mutation status of small lung cells in patients whose tissue and liquid re biopsy results do not meet the expectations and guide the follow-up treatment selection of patients.

4. Pathological analysis of artificial intelligence fiberoptic bronchoscopy combined with hesperidin derivatives

4.1. Expression analysis of C5orf34 in lung under fiberoptic bronchoscopy

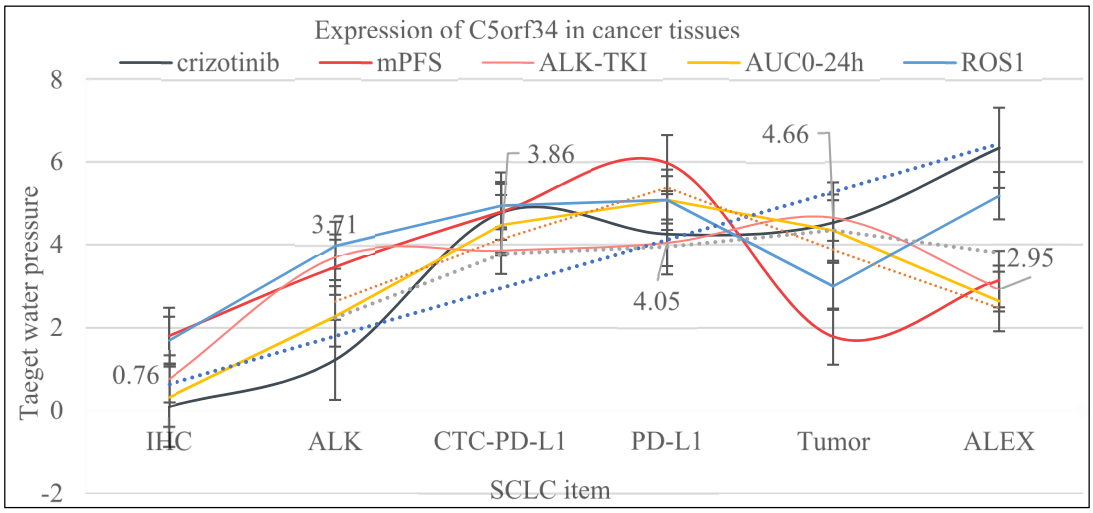

Figure 1. Expression of C5orf34 in cancer tissues.

As shown in Figure 1, the expression of C5orf34 in cancer tissues was significantly higher than that in adjacent tissues. The C5orf34h score of 35 patients with SCLC was less than 0.5 in 38 cases, and more than 1.5 in 2 cases. The score of C5orf34 in tumor was significantly higher than that in normal lung tissue ($P < 0.001$).

Table 1. The role of dynamic changes of H-FBS in evaluating treatment response.

Item	Crizotinib	mPFS	ALK-TKI	AUC0-24h	ROS1
IHC	0.09	1.8	0.76	0.32	1.69
ALK	1.22	3.47	3.71	2.27	4
H-FBS	4.78	4.8	3.86	4.48	4.95
PD-L1	4.26	5.98	4.05	5.09	5.09

As shown in Table 1, the role of dynamic changes of H-FBS in the evaluation of treatment response is generally due to the difficulty in obtaining tumor tissue and the dynamic changes of PD-L1 in the process of immunotherapy. The detection of PD-L1 expression in tumor tissue based on IHC cannot be used to dynamically evaluate the biological characteristics of tumor in the process of immunotherapy. H-FBS detection based on liquid biopsy can make up for the shortcomings of traditional detection methods, and can provide more important information about drug resistance and efficacy evaluation of tumor.

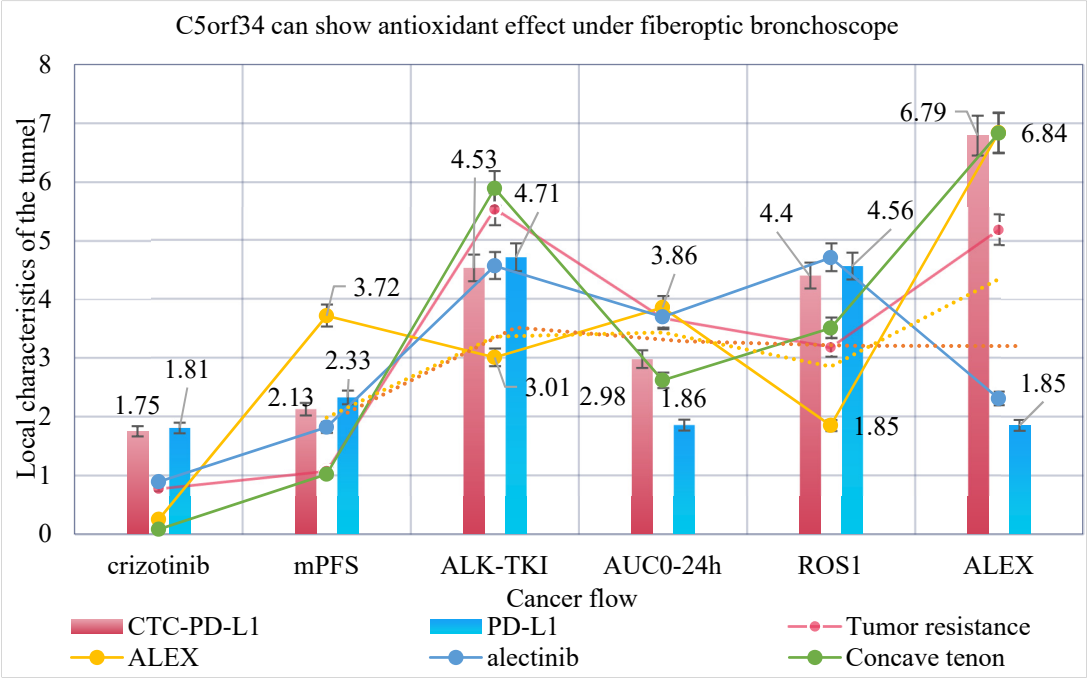

Figure 2. C5orf34 can show antioxidant effect under fiberoptic bronchoscope.

As shown in Figure 2, C5orf34 can show antioxidant effect under fiberoptic bronchoscopy, and the effect index is obvious. C5orf34 is recommended by many guidelines as the first-line treatment for SCLC patients with ALK gene mutation. Previous studies have shown that C5orf34 has a significant survival benefit in patients with ALK rearrangement positive SCLC and poor PS, regardless of the presence of central nervous system metastasis. As shown in Table 2, C5orf34 can bring significant PFS benefits compared with Crizotinib.

Table 2. C5orf34 can bring significant PFS benefits compared to Crizotinib.

Item	H-FBS	PD-L1	Tumor resistance	ALEX	alectinib	Concave tenon
Crizotinib	1.75	1.81	0.77	0.25	0.89	0.08
mPFS	2.13	2.33	1.07	3.72	1.82	1.02
ALK-TKI	4.53	4.71	5.53	3.01	4.57	5.89
AUC0-24h	2.98	1.86	3.67	3.86	3.7	2.62
ROS1	4.4	4.56	3.18	1.85	4.71	3.51
ALEX	6.79	1.85	5.18	6.84	2.31	6.83

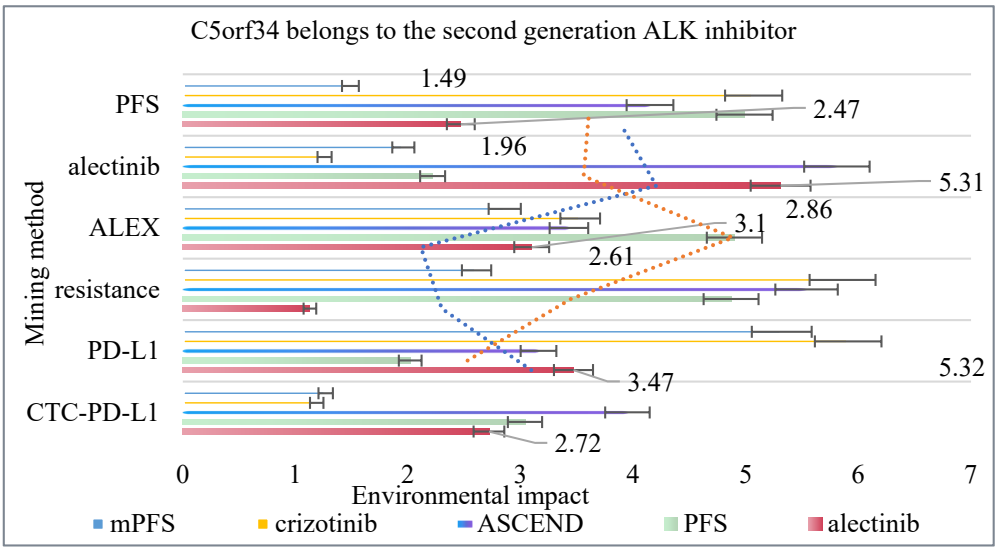

Figure 3. C5orf34 belongs to the second generation ALK inhibitor.

As shown in Figure 3, compared with the first-line chemotherapy, the fasting treatment of 750 mg C5orf34 for ALK positive patients with advanced SCLC significantly prolonged the MPFs by 16.6 months. Based on the ascend-4 study, the ascend-8 study was further carried out. The randomized, open-label Phase I elevation study 8 is a dose-optimized study. C5orf34 belongs to the second generation ALK inhibitors. Studies have shown that C5orf34 as a first-line treatment for ALK-positive advanced SCLC is highly effective and has a specific ability to enter the brain.

Table 3. Efficacy and safety of ALK-positive advanced SCLC.

Item	PFS	ASCEND	mPFS	C5orf34
H-FBS	3.04	3.95	1.27	3.5
PD-L1	2.02	3.16	5.32	5.57
ALEX	4.9	3.43	2.86	3.92
Cmax	2.22	5.81	1.96	5.87
PFS	4.99	4.15	1.49	1.62

As shown in Table 3, we evaluated the efficacy and safety of C5orf34 at 450 mg or 600 mg with

meal compared with 750 mg on an empty stomach in patients with ALK positive advanced SCLC. The pharmacokinetic results showed that compared with 750 mg fasting, 450 mg with meal increased auc0–24 h by 4.0%, and Cmax by 3%. The compliance of 450 mg group was better, and the median relative dose concentration was 100%. The median follow-up period was 14.3 months in the 450 mg group. The MPFs of the 750 mg fasting group and the 600 mg group were 12.2 months and 17.0 months, respectively. Conclusion: Ceritinib 450 mg with meal can reduce gastrointestinal toxicity and improve the curative effect.

4.2. Efficiency analysis of artificial intelligence fiberoptic bronchoscopy combined with hesperidin derivative detection

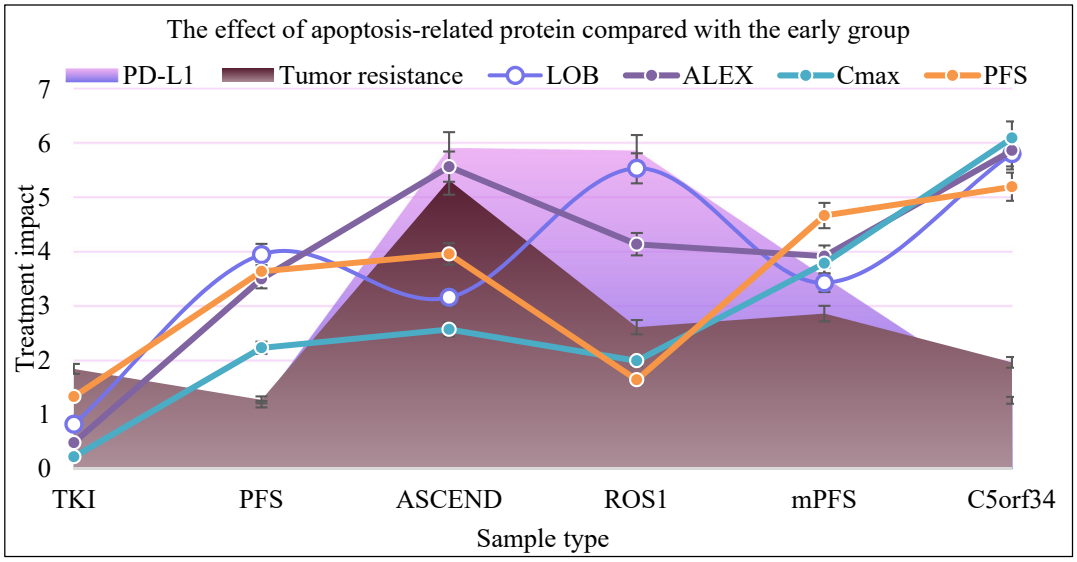

Figure 4. The effect of apoptosis-related protein compared with the early group.

As shown in Figure 4, Brigatinib is effective in the treatment of C5orf34 or Crizotinib resistant SCLC. Lob belongs to the third generation of ALK-TKI, studies have shown that lob has good clinical effect on SCLC patients with TKI refractory ALK+ or ROS1+, and it also shows promising effect in patients with known lung cancer metastasis.

As shown in Figure 5, artificial intelligence fiber bronchoscopy can directly obtain the imaging information of the tumor, and provide an objective and accurate evaluation for confirming the diagnosis and next-step treatment. Biopsy, brushing, needle aspiration biopsy, flushing, lung biopsy through bronchoscope X-ray positioning can be used to obtain tissue cells through forceps under direct vision, so as to facilitate pathological diagnosis. The rapid development of specific immunotherapy has achieved gratifying results, but its benefits are limited, and there are many difficulties, such as increasing drug resistance, frequent and uncontrollable adverse reactions, high cost, efficacy bottleneck, unclear prevention and metastasis, which hinder its further development. The active prevention of adverse reactions is a big problem in immunotherapy nowadays. It is a direction that can be considered to pretreat patients, or to build a curative effect prediction model from the perspective of immune imbalance, and to clarify the characteristics of suitable population.

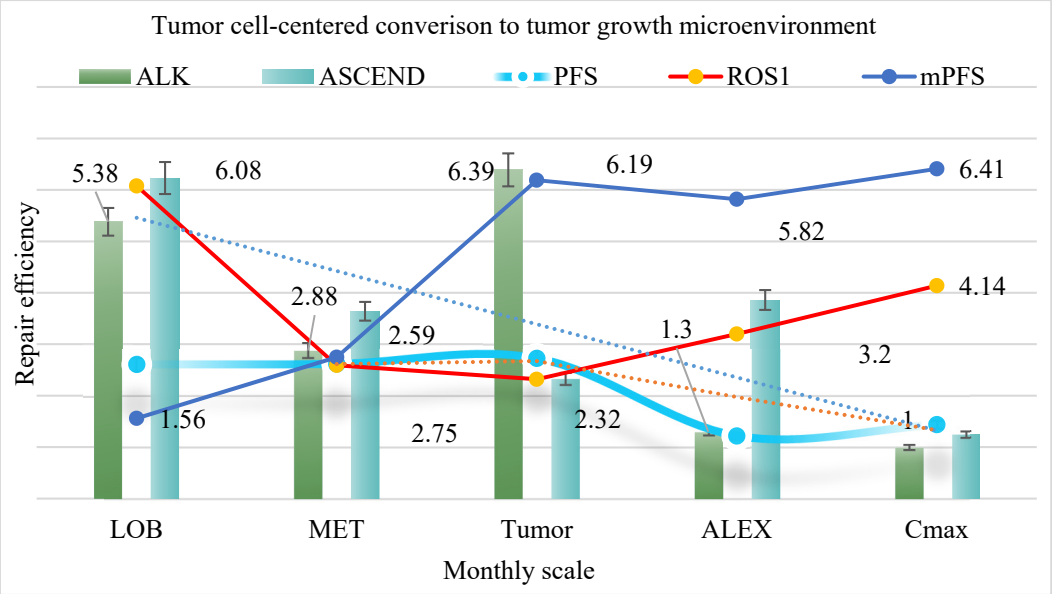

Figure 5. Tumor cell-centered conversion to tumor growth microenvironment.

Table 4. Targets with low mutation rates such as HER2.

Item	LOB	MET	Tumor resistance	ALEX	Cmax	PFS
ALK	0.82	0.89	1.84	0.48	0.22	1.33
PFS	3.95	1.19	1.27	3.5	2.23	3.64
ASCEND	3.16	5.91	5.32	5.57	2.57	3.96
ROS1	5.54	5.86	2.61	4.14	1.99	1.64
mPFS	3.43	3.53	2.86	3.92	3.79	4.67
C5orf34	5.81	1.26	1.96	5.87	6.1	5.2

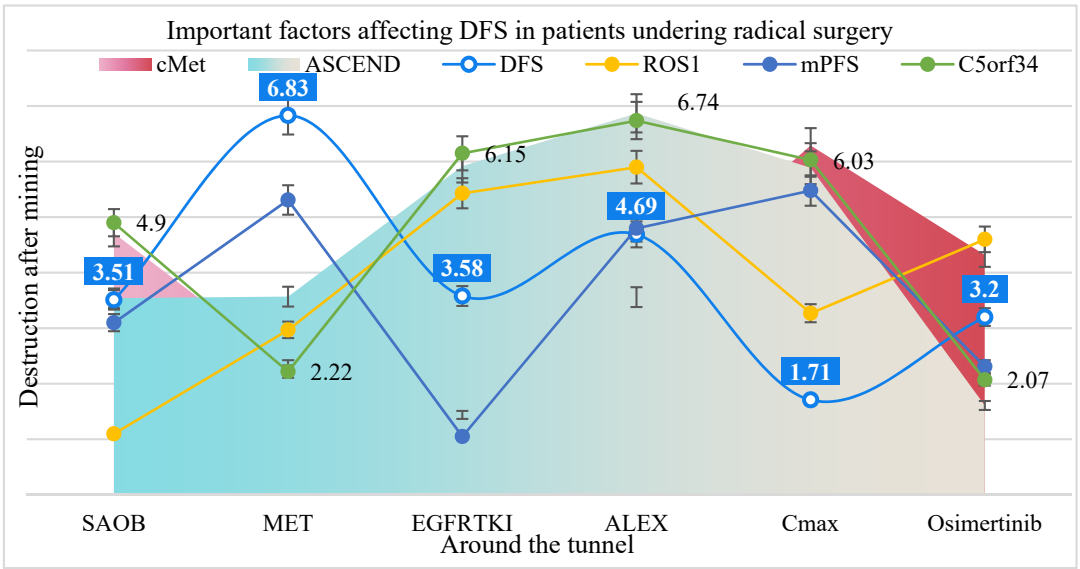

Figure 6. Important factors affecting DFS in patients undergoing radical surgery.

As shown in Table 4, for the targets with low mutation probability such as ALK, met and HER2, the survival rate of patients in the past chemotherapy era was extremely low. In recent years, new research and development drugs for these targets have been put into clinical trials and showed encouraging efficacy. This paper reviews the latest relevant Research on ALK, met and HER2 targets, so as to provide more reference for clinical treatment Good choice and theoretical basis.

Table 5. Osimertinib combined with SAOB treatment due to MET mutation.

Item	cMet	DFS	ASCEND	ROS1	mPFS	C5orf34
SAOB	0.82	3.95	3.16	5.54	3.43	5.81
MET	0.89	1.19	5.91	5.86	3.53	1.26
EGFRTKI	1.84	1.27	5.32	2.61	2.86	1.96
ALEX	0.48	3.5	5.57	4.14	3.92	5.87
Cmax	0.22	2.23	2.57	1.99	3.79	6.1
Osimertinib	1.33	3.64	3.96	1.64	4.67	5.2

As shown in Figure 6, C5orf34 is an important factor affecting DFs in patients with non-small cell lung cancer undergoing radical surgery. The 1, 2 and 3-year DFS rates of patients with positive C5orf34 were 57.00%, 41.20% and 23.20%, respectively. The median DFS time was 18 months. The 1, 2 and 3-year DFS rates were 89.40%, 62.60%, and 47.40% in C5orf34 negative patients. Saob is a novel small molecule selective CMET inhibitor. Previous animal experiments have shown that saob has good antitumor activity. As shown in Table 5, osimertinib combined with saob shows good clinical antitumor activity in the treatment of SCLC patients with met mutation leading to egfrtki treatment failure.

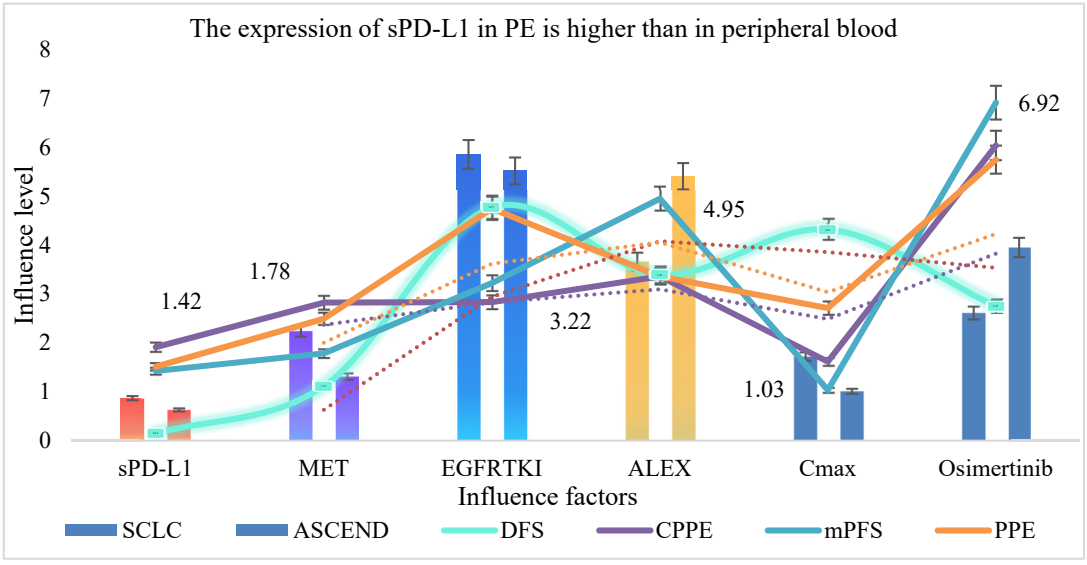

Figure 7. The expression of sPD-L1 in PE is higher than in peripheral blood.

As shown in Figure 7, the expression of spd-l1 in PE of the same patient was higher than that in peripheral blood, and its sensitivity and specificity for MPE diagnosis were also significantly

improved. CRP can be used to distinguish whether pneumonia patients complicated with pleural infection, and to distinguish between simple parapneumonic pleural effusion (uppe) or complex parapneumonic pleural effusion (CPPE). Zhao Jun et al. found that CRP level in PPE was significantly higher than that in SCLC in infectious PE, suggesting the value of CRP in the differential diagnosis of infectious PE.

Table 6. PE expresses more ITLN-1 than plasma.

Item	SCLC	DFS	ASCEND	CPPE	mPFS	PPE
sPD-L1	0.86	0.14	0.63	1.91	1.42	1.51
MET	2.24	1.11	1.31	2.82	1.78	2.49
EGFRTKI	5.86	4.77	5.52	2.83	3.22	4.75
ALEX	3.66	3.39	5.41	3.36	4.95	3.36
Cmax	1.72	4.32	1.01	1.61	1.03	2.71
Osimertinib	2.61	2.75	3.95	6.04	6.92	5.75

As shown in Table 6, the expression of itln-1 in PE is higher than that in plasma, and there is no correlation between serum and the expression level of itln-1 in PE; the expression level of itln-1 in patients with epithelioid MPM is higher than that in patients with lung cancer and tuberculosis. This study provides a new possibility for the differential diagnosis of epithelioid MPM by immunohistochemistry in the future. At present, the research on ITLN is mainly focused on animal model and cell level, and the mechanism of ITLN in human body is still rare. Its diagnostic value in PE is also worth further exploration.

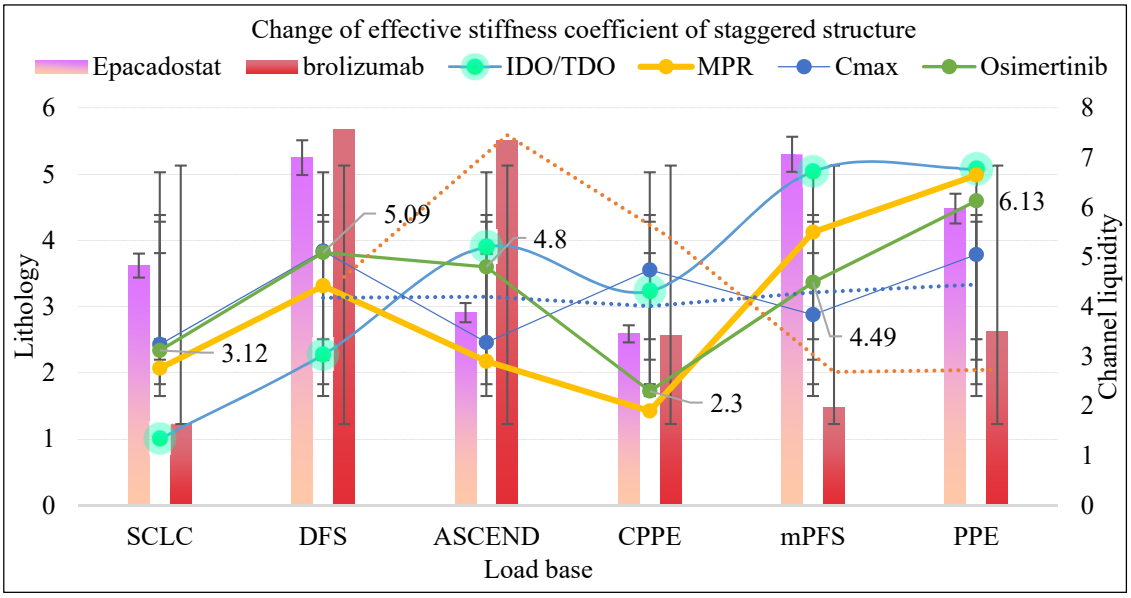

Figure 8. Change of effective stiffness coefficient of staggered structure.

As shown in Figure 8, the molecular mechanism of these checkpoint inhibitors is being studied or early clinical studies are being carried out. A large number of phase I to III clinical trials of IDO

inhibitors combined with chemotherapy and targeted therapy are being studied. Some studies have shown that Ido/TDO pathway blocking combined with radiotherapy and chemotherapy can improve the efficacy of radiotherapy and chemotherapy. However, the phase III clinical trial of epacadostat combined with PEM brolizumab was terminated early because it did not achieve the expected effect. Because of its high specificity, small side effects and other characteristics, now gradually from the basic experiment to clinical application, and in a variety of malignant tumors and blood disease treatment has achieved significant curative effect. As shown in Table 7, SCLC is more inclined to surgical treatment, but cancer vaccine is also an important research direction of cancer treatment. Neoadjuvant therapy may be more effective than adjuvant therapy, but there are still some problems, such as the timing of surgery and neoadjuvant immunotherapy, how to monitor and evaluate the therapeutic effect, and the treatment of adverse reactions. However, due to the limited experimental data, it has not been widely used in clinic.

Table 7. SCLC is more inclined to surgical treatment in treatment.

Item	Epacadostat	brolizumab	IDO/TDO	MPR	Cmax	Osimertinib
SCLC	3.62	1.23	1.35	2.76	3.24	3.12
DFS	5.25	5.67	3.04	4.42	5.12	5.09
ASCEND	2.91	5.51	5.21	2.9	3.28	4.8
CPPE	2.59	2.56	4.32	1.9	4.74	2.3
mPFS	5.3	1.47	6.73	5.5	3.84	4.49
PPE	4.48	2.63	6.78	6.65	5.05	6.13

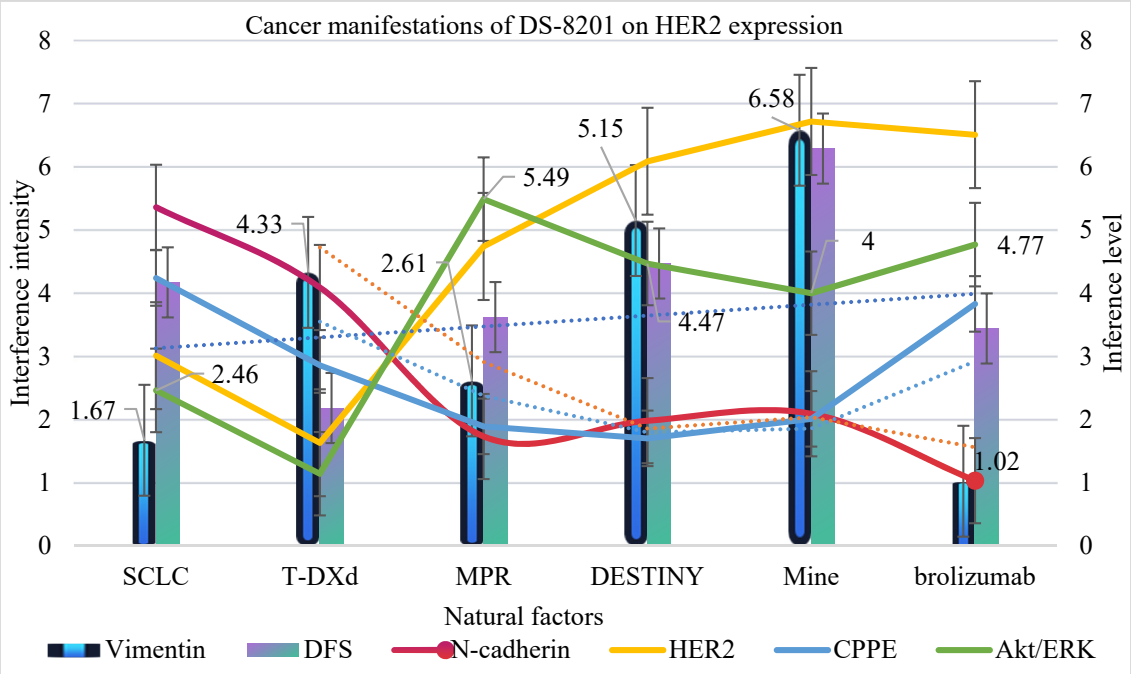

Figure 9. Cancer manifestations of DS-8201 on HER2 expression.

As shown in Figure 9, DS-8201 shows acceptable safety and potential therapeutic effect on

HER2 expressing cancer, with a wide range of therapeutic indexes. According to the results of phase I clinical trials previously published, the confirmed orr of T-DXd in the treatment of HER2 mutation by SCLC was 72.7%. The study group received T-DXd (6.4 mg/kg) for non-squamous SCLC patients with HER2 overexpression or HER2 activated mutation.

Table 8. SCLC has a higher pathological complete remission.

Item	Vimentin	N-cadherin	DFS	HER2	CPPE	Akt/ERK
SCLC	1.67	5.36	4.17	3.01	4.24	2.46
T-DXd	4.33	4.09	2.18	1.63	2.86	1.14
MPR	2.61	1.73	3.62	4.74	1.89	5.49
DESTINY	5.15	1.98	4.47	6.09	1.7	4.47
Mine	6.58	2.09	6.29	6.72	2.01	4
brolizumab	1.02	1.03	3.44	6.51	3.83	4.77

As shown in Table 8, SCLC has a high pathological complete response (PCR) and pathological major response rate (MPR), but the number of study cases is only 48. Other similar studies are also small phase II single arm studies. Whether SCLC can become a standard treatment still needs the data of randomized controlled trials.

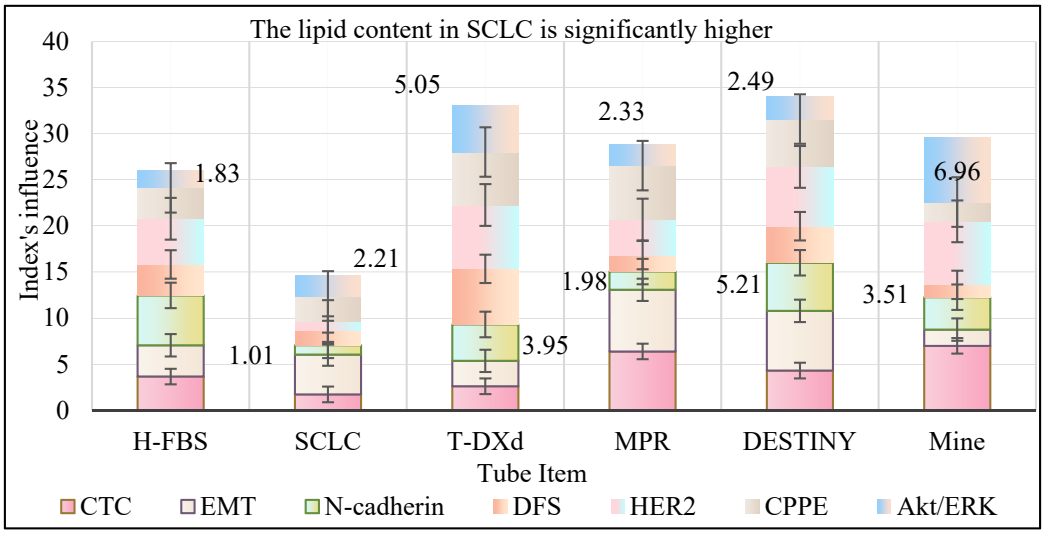

Figure 10. The lipid content in SCLC is significantly higher.

As shown in Figure 10, the diagnostic accuracy of this method is 97.9%, which is higher than that of lung biopsy (89%); compared with multiple CTC detection, this method has low cost and short time. Moreover, the lipid content in SCLC was significantly higher than that in PE group, and the amino acid content in MPE group was also significantly lower. On the other hand, it shows that H-FBS is feasible to recognize small molecule biochemical characteristics in different types of PE, and has a good application prospect.

5. Conclusions

H-FBS expression detection has a broad application prospect in predicting the efficacy of SCLC immunotherapy, especially in the process of dynamic monitoring of disease changes and evaluation of treatment response. The development of H-FBS detection technology can help us understand the immunotherapy of SCLC more comprehensively. At present, the related research of H-FBS is still in the primary stage, and the detection of small state cells in peripheral blood is usually used in clinic, but the diagnostic value is not significant. In conclusion, the diagnostic value of small cells in PE for SCLC is still controversial. Therefore, it is suggested that different tumor markers in serum should be tested together, but the accuracy of using one tumor marker alone is not enough. It was found that the combination of multiple tumor markers had higher sensitivity and specificity for the diagnosis of MPE, such as carbohydrate antigen-211 (ca211)/CEA combined with soluble mesothelin related peptide, the sensitivity for the diagnosis of malignant pleural mesothelioma was 93.8%.

With the development of SCLC targeted therapy, it can be said that great achievements have been made, and the research and development of new targeted drugs emerge in endlessly. Great progress has been made in molecular and immunological diagnosis of lung cancer. In addition to EGFR, new molecular targets, such as ALK, ROS1, met, ntrk and HER2, have been continuously detected, which promotes the development of new therapies. Many clinical trials of targeted therapeutic drugs are in progress and have shown promising and exciting results. These trials help redefine the role of targeted therapies in the treatment of lung cancer. Targeted therapy can ultimately change the mode of treatment for lung cancer and provide hope for patients with limited treatment options. We are moving towards biomarker-driven personalized treatment strategies to identify selected drug candidates that can benefit from existing therapies.

Because the rare mutations of EGFR are inconsistent with the efficacy of EGFR-TKIs, the research results are inconsistent.

This may be because EGFR has rarer mutation sites and different combination types. It is believed that with the popularization of direct sequencing methods, more unknown mutation sites will be discovered, which also brings greater challenges to the research of rare EGFR mutations. In addition, most previous studies focused on the relationship between the status of rare EGFR mutations and EGFR-TKIs. However, ignoring the effect of EGFR gene expression levels on the prognosis of patients receiving EGFR-TKIs may be one of the reasons for the contradictory results. In addition, selection bias and small sample studies may also cause inconsistent results.

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Conflict of interest

The authors declare there is no conflict of interest.

References

1. O. Arrieta, Z. L. Zatarain-Barrón, A. F. Cardona, New opportunities in a challenging disease: Lurbinectedin for relapsed small-cell lung cancer, *Lancet Oncol.*, **21** (2020), 605–607.
2. M. Dómine, T. Moran, D. Isla, J. L. Martí, I. Sullivan, M. Provencio, et al., SEOM clinical guidelines for the treatment of small-cell lung cancer (SCLC) (2019), **22** (2020), 245–255.
3. J. Trigo, V. Subbiah, B. Besse, V. Moreno, R. López, M. A. Sala, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial, *Lancet Oncol.*, **21** (2020), 645–654.
4. B. J. Morrison, J. C. Morris, J. C. Steel, Lung cancer-initiating cells: a novel target for cancer tlierapy, *Targeted Oncol.*, **8** (2013), 159–172.
5. V. S. Donnenberg, A. D. Donnenberg, Multiple drug resistance in cancer revisited: the cancer stem cell hypothesis, *J. Clin. Pharmacol.*, **45** (2005), 872–877.
6. G. Gehling, B. Beck, A. Caauwe, B. D. Simons, Defining the mode of tumour growth by clonal analysis, *Nature*, **488** (2012), 527–530.
7. H. T. Neagu, c-Kit expression in human normal and malignant stem cells prognostic and therapeutic implications, *Leuk. Res.*, **33** (2009), 5–10.
8. D. Burgos-Ojeda, B. R. Rueda, R. J. Buckanovich, Ovarian cancer stem cell markers: prognostic and therapeutic implications, *Cancer Lett.*, **322** (2012), 1–7.
9. S. Ali, S. Ali, Role of c-kit/SCF in cause and treatment of gastronintestinal stomal tumors (GIST), *Gene*, **40** (2007), 38–45.
10. L. Boldrini, S. Ursino, S. Gisfredi, P. Faviana, V. Donati, T. Camacci, et al., Expression and mutational status of c-kit in small-cell lung cancer: prognostic relevance, *Clin. Cancer Res.*, **10** (2004), 4101–4108.
11. G. Karoubi, L. Cortes-Dericks, M. Gugger, D. Galetta, L. Spaggiari, R. A. Schmid, Atypical expression and distribution of embryonic stem cell marker, OCt4, in human lung adenocarcinoma, *J. Surg. Oncol.*, **102** (2010), 689–698.
12. X. Zhang, B. Han, J. Huang, B. Zheng, Q. Geng, F. Aziz, et al., Prognostic significance of OTC4 expression in adenocarcinoma of the lung, *Jpn. J. Clin. Oncol.*, **40** (2010), 960–966.
13. L. M. Sholl, K. B. Long, J. L. Hornick, SOX2 expression in pulmonary non-small cell and neuroendocrine carcinomas, *Appl. Immunohistochem. Mol. Morphol.*, **18** (2020), 55–61.
14. T. Hussenet, S. du Manoir, SOX2 in squamous cell carcinoma: amplifying a pleiotropic oncogene along carcinogenesis, *Cell Cycle*, **9** (2010), 1480–1486.
15. K. C. Chou, The problem of Elsevier series journals online submission by using artificial intelligence, *Nat. Sci.*, **12** (2020), 37–38.
16. C. J. Langer, V. Hirsh, A. Ko, M. F. Renschler, M. A. Socinski, Weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: analysis of safety and efficacy in patients with renal impairment, *Clin. Lung Cancer*, **16** (2015), 112–120.

17. D. W. Cockcroft, H. Gault, Prediction of creatinine clearance from serum creatinine, *Nephron*, **16** (1976), 31–41.
18. H. G. Eichler, S. X. Kong, W. C. Gerth, P. Mavros, B. Jönsson, Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge?, *Value Heal*, **7** (2004), 518–528.
19. H. Tan, J. Hu, S. Liu, Efficacy and safety of nanoparticle albumin-bound paclitaxel in non-small cell lung cancer: a systematic review and meta-analysis, *Artif. Cells Nanomed. Biotechnol.*, **47** (2019), 268–277.
20. E. R. Gardner, W. L. Dahut, C. D. Scripture, J. Jones, J. B. Aragon-Ching, N. Desai, et al., Randomized crossover pharmacokinetic study of solvent-based paclitaxel and nab-paclitaxel, *Clin. Cancer Res.*, **14** (2008), 4200–4205.
21. M. A. Socinski, I. Bondarenko, N. A. Karaseva, A. M. Makhson, I. Vynnychenko, I. Okamoto, et al., Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial, *J. Clin. Oncol.*, **30** (2012), 2055–2062.
22. F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, A. Jemal, Globalcancer statistics 2018: GLOBOCAN estimates of incidence andmortality worldwide for 36 cancers in 185 countries, *CA Cancer J. Clin.*, **68** (2018), 394–424.
23. F. M. Watzka, C. Fottner, M. Miederer, A. Schad, M. M. Weber, G. Otto, et al., Surgi-cal therapy of neuroendocrine neoplasm with hepatic metasta-sis: patient selection and prognosis, *Langenbecks Arch. Surg.*, **400** (2015), 349–358.
24. J. F. Gainor, A. M. Varghese, S. H. I. Ou, S. Kabraji, M. M. Awad, R. Katayama, et al., ALK rear-rangements are mutually exclusive with mutations in EGFR orKRAS:an analysis of 1 683patients with non-small cell lungcancer, *Clin. Cancer Res.*, **19** (2013), 4273–4281.
25. A. T. Shaw, B. Y. Yeap, M. Mino-Kenudson, S. R. Digumarthy, D. B. Costa, R. S. Heist, et al., Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK, *J. Clin. Oncol.*, **27** (2009), 4247–4253.

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