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Review Article

Research Progress of Pleural Invasion in Non-Small Cell Lung Cancer

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Abstract

Visceral pleural invasion (VPI) is a poor prognostic factor of non-small cell lung cancer (NSCLC). 5-year overall survival was reported to be significantly higher in patients with PL0 (tumors in subpleural parenchyma or pleural junction tissue invading the pleural elastic layer) than in patients with PL1 (tumors invading the visceral pleural elastic layer) and PL2 (tumors invading the visceral pleural surface) (75.9%) *vs*. (63.6%) *vs*. (54.1%). Therefore, accurate diagnosis and active treatment of VPI are of great significance to improve the prognosis of NSCLC patients. At present, b-ultrasound, CT examination and other methods can be used in clinical prediction, histological diagnosis is the gold standard of VPI diagnosis. Age, gender, lymph node metastasis, pathological type and EGFR (+) are considered to be correlated with the occurrence of VPI and can be used as risk factors for the occurrence of VPI in NSCLC patients. Lobectomy plus systematic lymph node dissection is the standard treatment for patients with stage I NSCLC, but the need for adjuvant chemotherapy is controversial. This article reviews the current status of diagnosis, clinicopathological features and treatment of VPI.

Keywords: NSCLC; VPI; Diagnosis; Clinicopathological features; Prognosis

Introduction

At present, the incidence and mortality of lung cancer are increasing year by year [1], and non-small cell lung cancer (NSCLC, hereinafter referred to as "lung cancer") accounts for about 85% of the total number of lung cancers [2]. With the development of medical screening methods, more and more cases of early NSCLC have been diagnosed [3]. The prognostic factors of early NSCLC include tumor size, lymph node metastasis and patient age, among which visceral invasion (VPI) is also one of the important prognostic factors [4]. Studies have shown that visceral pleura invasion is an independent adverse prognostic factor for stage IB [5]. In The staging criteria of The International Association for The Study of Lung Cancer (IASLC) Lung Cancer Eighth Edition [6], TNM staging system is an important basis for evaluating. The prognosis of Lung Cancer. This is true even for small tumors with a maximum diameter ≤3cm. When visceral pleural invasion occurs, tumor stage is raised from T1 to T2, and lung cancer stage is raised from IA (T1N0M0) to IB (T2N0M0), which is a key staging node for lung cancer. Adjuvant chemotherapy is often used for patients with stage IB non-small cell lung cancer after complete resection. At present, there is no sufficient evidence to prove the value of adjuvant chemotherapy for patients with Stage IA non-small cell lung cancer. Therefore, accurate determination of the existence of VPI plays a crucial role in accurate staging, treatment decision and prognosis of NSCLC patients.

The Examination Method of VPI

The visceral pleura are composed of four layers: (1) Mesenchymal cell layer; (2) Intersubcutaneous connective tissue layer; (3) Elastic fiber layer; (4) The connective tissue layer separates elastic fibers from pulmonary parenchyma. At present, b-ultrasound, CT examination and other methods can be used in clinical prediction; histological diagnosis has become the gold standard of VPI diagnosis.

Imaging diagnosis

Imaging methods to diagnose VPI include B ultrasound, CT and MRI. In 1986, Wu Huaishen et al. [7] reported that the diagnostic rate of B-ultrasound comparison between X-ray and CT could reach 62% in terms of showing the relationship between tumor and pleura and tumor moving with respiration. Through B-ultrasound examination, changes in the tumor front and visceral pleura echo can be observed, as well as the situation of the tumor and visceral pleura during respiratory movement [8]. Although there are partial characteristic ultrasonic manifestations of peripheral lung cancer invading the pleura and chest wall, misjudgment can still be caused due to the influence of various factors. These factors include respiratory movement, tumor location, limited observation range, and subjective observation of the observer, etc. However, B-ultrasound still has advantages in preoperative evaluation of lung cancer patients with masses close to the chest wall and suspected visceral pleura or chest wall invasion. In 1985, another scholar [9] proposed that pleural invasion could be predicted by computed tomography (CT), pointing out that the methods and standards of prediction are different when the relationship between tumor and pleural position is different. VPI is more likely to exist when the tumor is directly connected to the pleura, and can be predicted by measuring and calculating the indexes on the corresponding CT images [9,10]. In 2021, Onoda H et al. [11] proposed a new concept in the study of the correlation between CT pleural markers and pulmonary pleural invasion in peripheral lung cancer: the bow linear marker between tumor and pleura, called bridging marker. Bridging markers are defined as a flat, twisted NSCLC tumor with an arched linear marker between the chest wall or

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interlobar fissure. In this study, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of bridging markers in the diagnosis of pulmonary pleural invasion were 88.9%, 83.5%, 83.7%, 18.6% and 99.4%, respectively. It was concluded that bridging markers were independent predictors of visceral pleural invasion. Glazer HS et al. [9] used CT to predict pleural invasion from the following three aspects: (1) Whether the lesion forms an obtuse Angle with the adjacent pleura; (2) Whether the length of the contact surface between the lesion and pleura >3cm; (3) Pleural thickening, that is, the obvious soft tissue plane formed between the lesion and pleura. Two or more positive indicators of the above three indicators were diagnosed as pleural invasion, and none or only one positive indicator was diagnosed as no pleural invasion. The sensitivity and specificity of the combined diagnosis of the three indicators were 87% and 59% respectively, while the accuracy was only 68%. Hsu JS et al. [12] used pleural markers of CT to predict VPI of non-adjacent non-small cell lung cancer. A total of 141 NSCLC patients were included, among which 44 (31.2%) were confirmed to have VPI by pathological analysis, and 97 (68.8%) had no VPI. Pleural markers are divided into 3 types (type 1, one or more linear pleural markers; Type 2, one or more linear pleural marks with a soft tissue component at the end of the pleura; Type 3, one or more soft tissue fascicular pleural markers are preferentially classified as type 3, type 2, and type 1 when more than one type is present. Results showed that no pleural markers had VPI, and the presence of type 2 pleural markers was moderately associated with VPI (accuracy, 71%; Sensitivity, 36.4%; Specificity, 92.8%). Pleural marker type 1 provided weak evidence for the exclusion of VPI (positive LR, 0.38). Pleural markers of type 3 showed the least likelihood of VPI (positive LR, 1.68). Studies have also shown that type 2 pleural markers on conventional CT images can improve the accuracy of early diagnosis of visceral pleural invasion in non-adjacent Pleural NSCLC. Between CT in tumor and pleural still often appear between pleural lung tissue sag, its pathological basis is tumor retraction and local pleural thickening and adhesion, these tumors of the distal and chest wall between linear shadow or small triangular shape, a typical sign pleural sag has important diagnostic value of peripheral lung cancer, sexual around this prompt CT in the diagnosis of lung cancer have a special meaning in [13]. Other studies showed that the pleural invasion rate of peripheral lung cancer with pleural depression was 65.2%, and the sensitivity, specificity and accuracy of pleural depression in the diagnosis of pleural invasion were 83.3%, 76.1% and 78.6%, respectively [14], which further provided an important basis for early detection and early diagnosis of VPI. In addition, Magnetic resonance imaging (MRI) can also play an important supplement and reference role in the diagnosis of VPI of lung cancer [15]. Some studies have reported the diagnostic method of parietal pleura or chest wall invasion using high-speed dynamic MRI of respiration [16], which is of clinical reference significance. Although some studies suggest that it may be superior to traditional CT in the diagnosis of lung cancer invading the chest wall, there is a lack of relevant research on VPI diagnosis using MRI at home and abroad, and further research is needed.

Histologic diagnosis

In 1988, whether the tumor broke through the elastic fiber layer of the visceral pleura was regarded as an important basis for whether the tumor invaded the pleura, and pathological diagnosis was the evaluation criterion for pleural invasion of lung cancer. Elastic fiber dyeing can clarify the relationship between the invasion of elastic fiber layer and the invasion of visceral pleura surface [17]. Elastic fiber staining in the diagnosis of lung cancer, pleural invasion: elastic fiber layer is one of the important anatomical marks dirty pleura, elastic fiber is mainly composed of elastin and micro fibrils, distribution in the alveolar interval, subcutaneous and large blood vessels, formation of alveolar structure of main frame, in maintaining the structure and function of the lungs bronchial and alveolar plays an important role. Conventional HE staining could not completely identify the visceral pleura invasion. Victoria blue staining (EFS) is often used for histological diagnosis of visceral pleura [18], which can well show the blue-black elastic fiber components in tissues. The principle is that some parts of elastic fibers are dyed blue and black by hydrogen bonding with the phenolic group of catechol in elastin dye. Zhao Lanxiang et al. [19] analyzed EFs staining and HE staining as the diagnostic basis for pleural invasion, and found that 28 of the 200 specimens with HE staining could not determine whether the pleural invasion was possible. EFs staining were more intuitive and could clearly determine whether tumor cells invaded the pleural layer, and reliable conclusions were finally drawn.

Clinicopathological Risk Factors for Visceral Pleural Invasion

Correlation between age and VPI

Deng H Y et al. [20] conducted a study on VPI related factors in NSCLC patients <3cm, which showed that the age of patients with VPI was significantly higher than that of patients without VPI (61.1 years: 56.1 years; Intraoperative, P <0.001). When patients were divided into two groups by age, the percentage of patients ≥60 years of age in VPI positive group was significantly higher than that in VPI negative group (57.4% *vs.* 36.9%; Intraoperative, 0.001). VPI is more likely to occur in NSCLC patients aged ≥60 years.

Correlation between gender and VPI

Zhang He [21] conducted a study on clinical characteristics of patients undergoing radical resection for stage IA-IIIA lung adenocarcinoma, including 505 patients (272 females and 233 males), of whom 266 (52.7%) developed VPI. The proportion of female PATIENTS with VPI was significantly higher than that without VPI (P=0.026). QiLP et al. [22] conducted a study on screening VPI predictors based on CT characteristics of NSCLC patients, which showed that the incidence ratio of female to male patients with VPI was about 3:2 (65:32 P =0.016). Deng H Y [20] showed no statistically significant difference between patients with VPI and patients without VPI (P =0.581). The above research results are inconsistent, and a large number of studies are still needed to clarify whether VPI is correlated with gender.

Correlation between lymph node metastasis and stage I VPI

Kudo et al. [23] found that the intrapleural lymphatic vessels in the visceral layer were unusually abundant, and there were interconnected networks arranged on the lung surface, which penetrated into the lung parenchyma and connected with the bronchial lymphatic vessels, and then drained to various lymph nodes in the hilum. Moreover, the study found that among patients

with NSCLC tumors ≤3 cm, especially those with tumors ≤2 cm, patients with VPI had more frequent lymph node metastasis than those without VPI (P=0.0003 and P=0.015). Shimizu et al. [24] also supported the view that tumor cells of VPI may enter mediastinal lymph nodes through the subpleural lymphatic vessels and hilar lymph nodes. Imai et al. [25] found that lymphatic vessels in the parietal subpleura could flow directly into the mediastinum without passing through hilar lymph nodes, resulting in skipping N2 metastasis. The tissue network between the visceral pleura and lymph nodes is more closely communicated, so patients with visceral pleura invasion are more likely to have lymph node metastasis. Yue Yuyan [26] suggested that VPI was correlated with lymph node metastasis. Zhang He [21] showed that for lung cancer ≤3cm, positive VPI was correlated with lymph node stage (N2) (P <0.001). Lymph node metastasis was associated with VPI. Patients with VPI ≤3cm NSCLC have a risk of lymph node metastasis, suggesting a poor prognosis. Lymph node metastasis is a risk factor for patients with VPI, which can be used as a basis for whether adjuvant chemotherapy is needed after surgery.

Correlation between histopathological types and VPI

Zhang He [18] showed that the incidence of VPI in squamous cell carcinoma patients was lower than that in the non-VPI group (15.5% *vs.* 4.5%, P <0.001). The reason why pleural metastasis of lung squamous cell carcinoma is less is considered to be that lung squamous cell carcinoma is mostly central lung cancer. There was no significant difference in the incidence of VPI between adenocarcinoma patients and VPI negative group (39.1% *vs.* 43.1%, P=0.367). However, QiLP studies showed [19] that adenocarcinoma was the main pathological type of VPI positive in NSCLC patients. Deng HY [20] showed that postoperative pathological findings of VPI in NSCLC were more likely to be adenocarcinoma (96.9% *vs.* 92.7%; P=0.097). The main pathologic types of VPI are still controversial, so it is necessary to further study the pathologic types of VPI positive patients in NSCLC.

Correlation between EGFR and VPI

Shi J et al. [27] collected clinicopathological characteristics and follow-up information of 508 consecutive surgically resected stage I-III NSCLC patients, and used RT-PCR to detect EGFR mutation. VPI with EGFR mutation was detected in 229 (45.1%) and 243 (47.8%) NSCLC patients. There was a significant correlation between EGFR mutation and VPI occurrence. Patients with VPI were divided into three groups according to their EGFR mutation status: EGFR wild-type, 19-DEL, and L858R. Compared with EGFR wild-type, 19-DEL (corrected OR =2.13, 95%CI =1.13 3.99, P=0.019) and L858R (corrected OR=2.89, 95% CI =1.59 5.29, P=0.001) significantly increased the risk of VPI. The frequency of L858R in VPI group was higher than that in VPI group (adjusted OR=2.63, 95% CI =1.42 4.88, P=0.002). It is concluded that different EGFR gene mutations have different risk of VPI.

Relationship Between VPI and Prognosis of NSCLC

Effect of VPI on prognosis of NSCLC in tumors of different sizes

VPI was discovered and reported by Brewer et al. [28] in 1958, and subsequent studies on the impact of VPI on prognosis have been controversial. At present, evidence-based medical evidence has confirmed that the frequency of VPI in NSCLC patients is 21% [29]. Long J [29] evaluated the role of VPI in patients with node-negative NSCLC of different tumor sizes, especially in stage IB disease. This study found a synergistic effect of VPI and tumor size on survival in patients with node-negative NSCLC. For stage IB non-small cell lung cancer patients with large tumors and VPI, adjuvant chemotherapy can be considered after surgical resection, and clinicians need to carefully conduct preoperative evaluation and postoperative follow-up. Further randomized clinical trials are needed to determine the effect of adjuvant chemotherapy on patients with stage IB NSCLC with VPI. Luo H et al. [30] found that VPI can affect the 5-year survival rate of patients with any primary tumor size, and the impact of VPI on survival increases with tumor size. When the tumor diameter was >3 cm, the prognosis of stage Ib or II A patients with VPI was relatively poor.

Effects of PL1 and PL2 on prognosis of NSCLC

The prognostic value of PL1 and PL2 for NSCLC is still controversial. Huang [31] believed that PL1 and PL2 are more important risk factors for recurrence and overall survival in patients with node-negative NSCLC than PL1 and PL2. The same conclusion was confirmed by Kudo et al. [23]. Adachi et al. [32]reported that PL1 and PL2 had no statistical difference in the recurrence rate and overall survival rate of patients without distinguishing whether there was lymph node metastasis. At present, the difference between PL1 and PL2 in the prognosis of NSCLC patients needs to be confirmed by large-scale studies.

Influence of different surgical methods on prognosis of NSCLC patients with VPI

Sccort et al. [33] studied the effect of different surgical methods on the prognosis of NSCLC patients with VPI. In the study, two different surgical methods of lobectomy and wedge resection of lung were observed in the treatment of elderly patients with stage IB NSCLC, and they found that compared with the wedge resection group, The operation time, chest tube drainage time and blood loss were significantly longer in the lobectomy group (P <0.05), but there were no significant differences in the incidence of postoperative complications, types of complications and length of hospital stay between the two groups (P >0.05). The overall survival rates of lobectomy group and wedge resection group were 76.9% (70/91) and 82.1% (32/39), respectively, and the recurrence rates were 32.9% (30/91) and 38.5% (15/39), respectively, with no statistical significance (P >0.05). It is concluded that wedge resection of lung can achieve long-term survival rate and recurrence control rate similar to lobectomy on the basis of preserving more lung tissue in elderly patients with stage IB NSCLC, which is worthy of clinical promotion.

Prognosis of stage IA and IB NSCLC surgery

1997 International TNM stage of lung cancer revised by the International Union against Cancer and the American Cancer Federation newly divided stage I NSCLC into two substages, Stage IA and Stage IB, because patients with these two substages had significant differences in long-term survival after surgical treatment [34]. According to the international TNM stage of lung cancer in 1997, T1 was the maximum diameter of the tumor ≤3cm, surrounded by visceral pleura. Fiberbronchoscopy confirmed that the tumor did not invade the proximal bronchial lobe. T2 was a tumor with one

of the following characteristics: (1) The maximum diameter of the tumor was >3cm; (2) The tumor invaded the main bronchus but was more than 2cm from the talar protuberant; (3) The tumor invaded the visceral pleura; (4) The primary tumor extended to the hilar region with atelectasis or obstructive pneumonia, but not to the whole lung. Lin Yidan et al. [35] retrospectively analyzed 96 patients with stage I NSCLC who underwent surgical treatment from 1974 to 1995 in the Thoracic surgery Center of Field Surgery Department, Military Medical Institute, Doping Hospital, Third Military Medical University. Univariate and multivariate analyses were performed on 9 factors that might affect long-term survival after surgery, including gender, age, T-grade, primary tumor size, visceral pleural invasion, resection method, tumor pathological type, degree of differentiation and location. Conclusion: There was a significant difference in 5-year survival rate between stage IA and IB NSCLC patients. Univariate analysis indicated that T grade, primary tumor size, visceral pleural invasion, and tumor differentiation degree had significant influence on 5-year survival rate of stage I NSCLC patients ($P < 0.05$). Multivariate analysis suggested that only VPI and tumor differentiation were independent prognostic factors ($P < 0.05$). Ichinose et al. [35] reported that the 5-year postoperative survival rate of patients with stage IA and IB NSCLC was 84.8% and 66.6%, respectively, 18.2% difference, while Mountain [35] reported that the 5-year postoperative survival rate was 67% and 57%, respectively, 10% difference. The significant difference in long-term survival between PATIENTS with STAGE IB and IA NSCLC is a common phenomenon, which is related to pleural invasion and independent of postoperative adjuvant therapy.

Treatment of NSCLC Patients with VPI

Lobectomy plus lymph node dissection is the standard treatment for patients with early NSCLC [33]. In patients with small tumor diameter, poor cardiopulmonary function, and peripheral lung lesions, pulmonary wedge resection may be a compromise option. There is still controversy over whether adjuvant therapy is needed for patients with stage I NSCLC complicated with high risk factors in NSCLC guidelines at home and abroad. The 2020 NCCN guidelines recommended adjuvant chemotherapy for stage IB NSCLC patients with high-risk factors [36]. This view has not been updated in the 2021 NCCN Guidelines [37]. However, the 2020 CSCO guidelines showed that adjuvant chemotherapy is generally not recommended for stage IB NSCLC (including lung cancer with high-risk factors) due to lack of high-level evidence support [38,39]. The CSCO guidelines of 2021 still hold this view [40,41]. Adjuvant therapy for Stage I-III NON-small cell lung cancer patients with EGFR-positive STAGE IB NSCLC after complete tumor resection can be considered (Recommended by Class IA evidence) according to guidelines for Adjuvant therapy after safe resection for Stage I-III non-small cell lung cancer (2021) issued by Lung Cancer Professional Committee of The Chinese Anti-Cancer Society. The recommendation is based on the global multicenter ADAURA study involving NSCLC patients after complete resection of stage IB to IIIA tumors. The study showed that adjuvant therapy with oxitinib for 3 years after complete resection of tumors reduced the risk of disease recurrence or death by 61% for stage IB patients with EGFR-positive mutations. For such patients, adjuvant therapy with oxitinib can be considered [42]. According to this guideline, adjuvant chemotherapy is not recommended for stage IB NSCLC patients with EGFR-positive mutation after complete tumor resection. For patients with high risk factors, multidisciplinary comprehensive evaluation is recommended, and postoperative adjuvant chemotherapy can be considered based on evaluation opinions and patient wishes. For stage IB NSCLC patients with EGFR mutation, randomized controlled clinical trials such as CALGB9633 [39] and JBR10 [43] and meta-analysis of LACECG [40] found that postoperative chemotherapy in stage IB NSCLC patients showed no significant survival benefit. Therefore, postoperative adjuvant chemotherapy is not routinely recommended for these patients. However, a retrospective study in 2013 [44] showed that some stage IB NSCLC patients could benefit from postoperative adjuvant chemotherapy. Therefore, for patients with high risk factors, multidisciplinary comprehensive evaluation is recommended to consider whether to undergo postoperative adjuvant chemotherapy based on the evaluation results and patients' wishes. In addition, more prospective studies on adjuvant chemotherapy in stage I NSCLC patients with VPI are needed to clarify the necessity of postoperative adjuvant chemotherapy in stage I NSCLC patients.

Summary and Outlook

Pleural invasion of lung cancer can be found by imaging examination, and pathology is the gold standard for the diagnosis of pleural invasion. Visceral pleural invasion is considered as an independent prognostic factor for NSCLC. Gender, age, pathological type and EGFR mutation status are correlated with the occurrence of VPI, which can be used as predictors of VPI in stage I NSCLC patients. At present, both domestic and foreign guidelines recommend surgical treatment for patients with pleural invasion of stage I NSCLC, but there is controversy over whether adjuvant chemotherapy should be performed after surgery. At present, the relationship between pleural invasion and more biological factors is not clear, such as the histological type of lung cancer, tumor growth rate, and tumor molecular characteristics KRAS mutation status. These will be the entry point for further research.

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