Review Article

Research progress in predicting visceral pleural invasion of lung cancer: a narrative review

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Background and Objective: In lung cancer, visceral pleural invasion (VPI) affects the selection of surgical methods, the scope of lymph node dissection and the need for adjuvant chemotherapy. Preoperative or intraoperative prediction and diagnosis of VPI of lung cancer is helpful for choosing the best treatment plan and improving the prognosis of patients. This review aims to summarize the research progress of the clinical significance of VPI assessment, the intraoperative diagnosis technology of VPI, and various imaging methods for preoperative prediction of VPI. The diagnostic efficacy, advantages and disadvantages of various methods were summarized. The challenges and prospects for future research will also be discussed.

Methods: A comprehensive, non-systematic review of the latest literature was carried out in order to investigate the progress of predicting VPI. PubMed database was being examined and the last run was on 4 August 2022.

Key Content and Findings: The pathological diagnosis and clinical significance of VPI of lung cancer were discussed in this review. The research progress of prediction and diagnosis of VPI in recent years was summarized. The results showed that preoperative imaging examination and intraoperative freezing pathology were of great value.

Conclusions: VPI is one of the adverse prognostic factors in patients with lung cancer. Accurate prediction of VPI status before surgery can provide guidance and help for the selection of clinical operation and postoperative treatment. There are some advantages and limitations in predicting VPI based on traditional computed tomography (CT) signs, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT and magnetic resonance imaging (MRI) techniques. As an emerging technology, radiomics and deep learning show great potential and represent the future research direction.

Keywords: Lung cancer; visceral pleural invasion (VPI); prediction

Submitted Jul 26, 2023. Accepted for publication Nov 17, 2023. Published online Dec 26, 2023.
doi: 10.21037/tcr-23-1318
View this article at: https://dx.doi.org/10.21037/tcr-23-1318

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Introduction

The Global Cancer Statistics 2020 estimated that lung cancer incidence was 11.4%, with lung cancer being the world's second most prevalent type of malignant tumor and the leading cause of cancer death, with an estimated 1.8 million deaths (18%) worldwide in 2020 (1). Visceral pleural invasion (VPI) refers to the invasion of tumor cells beyond the pleural elastic fiber (EF) layer, which is one of the most important adverse prognostic factors for lung cancer, and it is also an important predictor of postoperative recurrence and lymph node metastasis (2-5). The eighth tumor-node-metastasis (TNM) staging system defines the pathological grade of pleural invasion as PL0–PL3, where PL0 is pleural invasion free and the tumor does not extend beyond the visceral pleural elastic layer, PL1 is tumor invasion beyond the elastic layer, PL2 is tumor invasion on the visceral pleural surface, and PL3 is tumor invasion of the parietal pleura and/or chest wall. VPI is graded as PL1 and PL2, and it is recommended that EFs staining should be evaluated when hematoxylin-eosin (HE) staining does not clearly distinguish PL0 from PL1 (6). Several studies have regarded the significance of accurate prediction and diagnosis of VPI for treatment decisions of lung cancer patients in the preoperative and intraoperative stages (7-18). Therefore, this review summarizes the recent research in predicting VPI. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1318/rc).

Methods

A non-systematic review of the latest literature to predict the status of VPI in lung cancer patients was carried out. Relevant articles in English available in the PubMed database as at 4 August 2022 were included. Search terms included ("VPI") AND ("Lung cancer" OR "CT" OR "^{18}F-FDG PET/CT" OR "MRI" OR "Radiomics" OR "Deep learning" OR "Pathology" OR "Prognosis") (*Table 1*).

Discussion

Clinical significance

VPI is more likely to develop hilar and mediastinal lymph node metastasis in lung cancer patients and is independently associated with skipping N2 metastasis (7,8). The International Association for the Study of Lung Cancer (IASLC) suggests that for patients with tumor size less than 3 cm and with VPI, the T stage of the TNM staging system increases from T1 to T2, and the TNM stage increased from IA to IB (6). However, the relationship between the pathological grade of VPI and both the prognosis of lung cancer patients and postoperative chemotherapy decision-making remains highly uncertain. Some scholars have studied the influence of VPI on the selection of adjuvant therapy and the prognosis of patients with lung cancer in different densities, sizes, and pathological grades of VPI. Okada *et al.* (9) reported that VPI (+) had adverse effects on the prognosis of solid nodules with cT1 size, but not on ground-glass nodules (GGNs). Liang *et al.* (10) demonstrated that non-small cell lung cancer (NSCLC) with tumor size ≤3 cm and VPI grade of PL1 should not be upgraded to the T2 stage, and postoperative adjuvant chemotherapy was not recommended when lymph node metastasis was negative. De Giglio *et al.* (11) implied that VPI (+) was not associated with poor

Table 1 The search strategy summary

Items	Specification
Date of search	4 August 2022
Databases and other sources searched	PubMed
Search terms used	("VPI") AND ("Lung cancer" OR "CT" OR "^{18}F-FDG PET/CT" OR "MRI" OR "Radiomics" OR "Deep learning" OR "Pathology" OR "Prognosis")
Timeframe	2000–2022
Inclusion and exclusion criteria	Inclusion criteria: original articles, review articles; written in English only
	Exclusion criteria: case reports, letters to the editor; non-English language
Selection process	Y.W. independently conducted the search; all the authors contributed to final version of the paper

prognosis for lung cancer with tumor size <4 cm and did not recommend adjuvant therapy. Adjuvant therapy is strongly recommended only when the tumor size is ≥4 cm and accompanied by lymph node metastasis and VPI (+). However, Qi *et al.* (12) reported that VPI (+) was an adverse prognostic factor for NSCLC with tumor size ranging from 3.1 to 4.0 cm, suggesting that the staging should be upgraded from pT2a to pT2b. Likewise, a recent study has indicated that early-stage NSCLC patients with tumor size ≤2 cm and VPI (+) have better long-term survival as compared to sublobectomy in patients with lobectomy (13). Sublobectomy is an independent risk factor for the recurrence of lung adenocarcinoma with tumor size ≤2 cm and VPI (+) (14). In patients with T1a tumors combined with VPI (+), the prognosis of the lobectomy group is better than that of the sublobectomy group (15). Therefore, further evaluation is required to confirm sublobectomy can be selected for early lung cancer and whether VPI exists before surgery would affect the surgical outcome. A recent study demonstrated that T1/VPI (+) tumors (stage IB) required more extensive lymph node dissection than T1/VPI (–) tumors (stage IA) (16). Therefore, the accurate prediction of the VPI can assist with the planning of surgical procedures of early lung cancer.

Intraoperative diagnosis of VPI

Takizawa *et al.* (17) calculated the accuracy of VPI diagnosis by conventional white light mode of thoracoscopy as 56.7%. In comparison, autofluorescence mode combined with thoracoscopy could improve the sensitivity, specificity, and accuracy of VPI diagnosis in NSCLC surgery. Xie *et al.* (14) reported that the accuracy, sensitivity, and specificity of intraoperative autofluorescence staining of frozen sections in the diagnosis of VPI of lung adenocarcinoma ≤2 cm were 95.5%, 86.8%, and 100%, respectively. Sawada *et al.* (18) calculated that the diagnosis accuracy of confocal laser endomicroscopy was as high as 86.7%. These findings are conducive to the decision-making of surgical intervention.

Preoperative prediction of VPI

Computed tomography (CT) signs

A high-resolution CT scan can display the position, morphology, and relationship between the nodules and neighboring structures in the lungs, which is crucial for the qualitative determination of pulmonary nodules. Recent studies have investigated the preoperative prediction of VPI in lung cancer with CT features (19-30). Qi *et al.* (19) included 205 cases of NSCLC of any size, which was found that gender, pleural indentation, tumor density, and minimum distance from the lesion to the pleura (DLP) were independent predictors of VPI. Yang *et al.* (20) included 52 cases of lung adenocarcinoma ≤3 cm, and found that a connection between nodules and non-interlobar fissure pleura with thick line shadow, accompanied by triangular high-density pleura at the pleura end (type III), direct contact between nodules and non-interlobar fissure pleura (type IV), or interlobar fissure pleura pulled by nodules (type I) or pushed and translocated (type III), had high diagnostic values in predicting VPI. In addition, a quantitative index called pleural indentation fraction (PIF) was first proposed in this study to evaluate the degree of pleural indentation. PIF was defined as the ratio of pleural displacement distance to the length of affected pleural projection. It was found that when the interlobar fissure pleura were pulled by nodules, PIF and DLP were significantly and linearly correlated. However, the sample size included in this study was small, and its conclusion needed to be confirmed by studies with large samples.

These studies included cases classified as "no contact between tumor and pleura, direct contact between tumor and pleura, and indirect contact between tumor and pleura", and found that pathological VPI did not occur when the tumor and pleura were not in contact. Several studies have analyzed the subtype of indirect contact between tumors and the pleura separately (21,22). Hsu *et al.* (21) included 141 cases of NSCLC of any size and indirect contact with the pleura, they defined the line or strip shadows between the tumor and pleura as the pleura tags and divided them into three types. Type I had one or more linear shadows that could be observed on the lung window, and there was no soft tissue component at the pleura end on the mediastinal window. Type II had one or more linear shadows that could be observed on the lung window, and there were soft tissue components on the pleural end of the mediastinal window. For type III, one or more strips of soft tissue shadows were observed on the mediastinal window. It was found that the type II pleura tags was moderately associated with VPI, with an accuracy of 71%, sensitivity of 36.4%, and specificity of 92.8%. This sign could improve the accuracy of preoperative prediction of VPI. However, this study was a single-center, small sample study, and did not further explore the pathological mechanism of various types of pleural tags. Onoda *et al.* (22) included 221 consecutive patients with NSCLC that did not appear touching the

pleural surface, ≤3 cm in solid tumor diameter. They proposed the bridge tag sign, which was defined as the flat distortion of the tumor caused by the arch-shaped linear tag between the tumor and pleura on CT. Multivariate logistic regression analysis found that the bridge tag sign significantly correlated with VPI, and pathological control found that bridge tag sign was related to the longer contact surface between the tumor and pleura under a light microscope and the trapezoidal shape of pleural indentation. The sensitivity, specificity, and accuracy of VPI diagnosis with the bridge tag sign were 88.9%, 83.5%, and 83.7%, respectively. Hence, the bridge tag sign could improve the accuracy of preoperative prediction of VPI of lung cancer ≤3 cm. The limitations of the study were that, this was a single-center, retrospective study consisting of a small number of cases with VPI-positive (only nine cases) and lead to the problem of sample imbalance, moreover, elastic staining was not necessarily performed in all cases. Hence, it was possible that minor VPI was underestimated.

Several other studies have analyzed the type of tumor in direct contact with the pleura separately (23-25). Hsu *et al.* (23) included 136 cases of NSCLC of any size, and found that the convex and obtuse angle between the tumor and pleural contact had a high positive predictive value (94%) and specificity (91%) for the prediction of pleural invasion, the sensitivity and accuracy of this sign in the diagnosis of pleural invasion were low at 57% and 45%, respectively. Ebara *et al.* (24) included 201 cases of lung cancer ≤3 cm (including two cases of small cell lung cancer). They studied the value of three-dimensional (3D) reconstruction classification of the relationship between the tumor and pleura in predicting pleural invasion in lung cancer and found that the 3D classification of "skirt-like" (wrinkling and thickening of pleura with indrawn) had the highest accuracy in predicting pleural invasion (77%). In addition, the ratio of tumor-pleural contact area to maximum tumor diameter was found to be the best predictor of parietal pleural invasion (PL3 grade) versus VPI (PL1, PL2 grade), with the highest recorded accuracy (77%) when the cut-off value was 13.4. However, 3D post-processing took a long time and the process of calculating the ratio was also complicated, which made its clinical application inefficient. Heidinger *et al.* (25) compared the incidence of VPI of solid nodules and GGNs in lung adenocarcinoma that were in direct contact with the pleura of ≤3 cm and considered the predicted risk factors of VPI in their respective CT signs. It was found that the incidence of VPI (+) of solid nodules was significantly higher than GGNs. In solid nodules, the ratio of contact length between nodules and pleura to nodule size and the combination of multiple types of pleural tail signs were correlated with VPI. In GGNs, the length of contact between the solid component and the pleura and the growth of the nodules into adjacent lung lobes or surrounding tissues were associated with VPI. This study was retrospective and the selection of samples may have been biased.

In addition, several studies have separately analyzed the risk factors of VPI in lung adenocarcinoma presenting as GGN (26-29). Zhao *et al.* (26) studied the clinical, pathological, and CT characteristics of 156 cases of lung adenocarcinoma ≤3 cm presenting as GGN, and found that VPI (+) can occur in both pure and mixed GGNs. VPI (+) was more common in GGNs >2 cm, and the incidence of VPI (+) in pure GGNs was 17.4% (12/69). The incidence of VPI (+) in mixed GGNS was 32.2% (28/87). The direct contact between nodules and pleura or pleural indentation sign found on CT could not reliably predict VPI status, and the probability of VPI (+) with PL2 level in GGNS was low. However, studies by Ahn *et al.* (27) and Zhao *et al.* (28) found that pure GGNs did not observe VPI (+). Ahn *et al.* (27) found that direct contact between tumor and pleura, pleura thickening, a solid component ratio greater than 50%, and maximum tumor diameter greater than 2 cm were independent predictors of VPI in 188 cases of T1-sized lung adenocarcinoma presenting as GGN. Kim *et al.* (29) included 404 patients with malignant subsolid nodule, they reported that the incidence of VPI (+) was the highest in subsolid nodules in direct contact with the pleura and accompanied by pleural indentation, and VPI (+) was associated with the recurrence of early lung cancer.

At present, many scholars have explored VPI prediction based on CT features, but its accuracy remains to be established. Kim *et al.* (30) performed a confirmatory study that included 695 patients with lung adenocarcinoma cT1N0M0, using a combination of CT features (CT-VPI) to predict VPI. The data could be categorized as follows: (I) CT-VPI1: where the tumor and contact length were greater than one-quarter of the tumor circumference; (II) CT-VPI2: CT-VPI1 or pleural retraction; (III) CT-VPI3: CT-VPI1 or thickened pleural tags sign at the pleural end; (IV) CT-VPI4: the presence of CT VPI1, pleural retraction sign, or thickened pleural tags sign at the pleural end. The results indicated that the diagnostic accuracy of these CT feature combinations ranged from 63% to 72%, and the accuracy of CT VPI1 was the highest. Positive predictive values were all low, ranging from 44% to 56%, suggesting that using

these CT features to predict VPI had a false positive rate of at least 50%. However, this study only analyzed CT signs that reflected the relationship between the tumor and pleura and did not include features representing the invasion of the tumor (e.g., tumor size, solid component size, etc.) as factors to predict VPI.

All the above studies were single-center retrospective studies, and there was inevitable selection bias. The interpretation of traditional CT features depended on the experience of radiologists, and there was a certain degree of subjectivity. Conclusions varied according to the inclusion criteria, and most of the sample sizes were relatively small. Therefore, it is necessary to comprehensively analyze clinical data, tumor CT signs, and the relationship between tumor and pleura, and perform stratified analysis according to tumor size, density, and the relationship between tumor and pleura. Using multivariate logistic regression analysis to construct a comprehensive prediction model, and testing its prediction efficiency on the basis of large samples and multiple centers. The value of CT features in predicting VPI of lung cancer can be clarified more clearly.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT

^{18}F-FDG PET/CT can perform functional imaging and display the morphological characteristics of the lesion by CT scan on the same machine. This combination reflects the metabolic and anatomical information of the lesion obtained simultaneously. Tanaka *et al.* (31) utilized ^{18}F-FDG PET/CT in predicting pleural invasion of 208 cases of lung adenocarcinoma in direct contact with the pleura. Multivariate analysis indicated that maximum standardized uptake value (SUVmax) and the obtuse angle between the tumor and pleura were independent risk factors for pleural invasion. SUVmax alone [area under the curve (AUC) =0.815] was more valuable in predicting pleural invasion than the multivariate model (AUC =0.819–0.829). In the subgroup analysis with tumor size ≤3 cm, multivariate analysis displayed that SUVmax and tumor-pleural contact length were independent predictors of pleural invasion in lung cancer, and only SUVmax (AUC =0.844) demonstrated similar diagnostic performance to the multivariate model (AUC =0.845–0.857). It should be noted that this study included pure GGNs and 11 cases of parietal pleural invasion, and only analyzed lung cancer with direct contact with the pleura which was a single type. Chen *et al.* (32) utilized ^{18}F-FDG PET/CT to predict VPI in lung adenocarcinoma presenting as GGN <3 cm. Multivariate analysis found that DLP and SUVmax were independent predictors of VPI, and the AUC value of VPI predicted by the combined model of the two variables was 0.90. The sensitivity and specificity of the model were 96.67% and 71.43%, respectively. Despite the good diagnostic efficacy of this model, the sample size of this study was small (65 cases), including 11 cases of pure GGNs, and the included lesions might not be related to the pleura. Therefore, the predictive efficacy of this model was high but not representative. Moreover, ^{18}F-FDG PET/CT examination was expensive and had limited clinical application value.

Magnetic resonance imaging (MRI) technique

MRI shows high resolution for soft tissue, and the relationship between the subpleural mass and the pleura can be established by using MRI. Therefore, a study was conducted to explore whether MRI could accurately predict VPI. Zhang *et al.* (33) retrospectively analyzed 3-T MRI T1WI enhanced examination images of 33 patients with NSCLC of any size, and the MRI technique used contrast-enhanced 3-T MRI with a free-breathing radial 3D fat-suppressed volumetric interpolated breath-hold examination (VIBE) pulse sequence. The ability of the tumor-pleural interface (smooth or irregular) in MRI to distinguish between PL1 and PL2 level of VPI was evaluated. Results revealed that 20 of 21 patients with PL1 had smooth edges and 10 of 12 patients with PL2 had irregular edges, with accuracy, sensitivity, and specificity of 91%, 83%, and 95%, respectively. However, this was the only study using the MRI technique to predict VPI in lung cancer. Despite the excellent diagnostic efficacy, this study included only a few cases, and a larger sample study and multi-sequence comparative analysis were required to fully validate the MRI technique. Although MRI can be used for multi-dimensional imaging, its shortcomings, such as long examination time and low spatial resolution of displaying lung tissue, limit the clinical application of MRI in the lung.

Histogram and texture analysis

The prediction of VPI in lung cancer based on traditional CT features has a certain value at the expense of strong subjectivity, therefore, some studies have explored the efficacy of image-based one-dimensional histogram features and texture analysis in predicting VPI of lung cancer (34,35). Zuo *et al.* (34) studied the preoperative prediction of VPI of cT1N0M0 lung adenocarcinoma based on CT texture characteristics, a total of 313 patients enrolled

from two independent institutions. Multivariate analysis found that 3D CT long diameter, skewness, sphericity, and combined chronic obstructive pulmonary disease (COPD) were independent risk factors for predicting VPI. Based on these risk factors, the AUC value of VPI was predicted to be 0.890 in the training set and 0.864 in the independent external verification set. The model reported a good discriminant ability and goodness of fit. Wei *et al.* (35) built a comprehensive model based on CT texture features and pathology-image features and included 221 patients with NSCLC ≤3 cm. Results displayed that mean tumor diameter, density type, classification of tumor-pleural relationship, and pathological lymph node metastasis status in the clinical model were independent risk factors for predicting VPI. The AUC values of VPI predicted by the internal validation centralized clinical model, texture feature model, and comprehensive model were 0.882, 0.824, and 0.894, respectively. However, this model included postoperative pathological lymph node status as a predictor and could not be used to predict VPI before surgery.

Radiomics

In recent years, radiomics has become a research hotspot. In comparison with histogram and texture analysis, radiomics provide more high-dimensional and otherwise unrecognizable in-depth information and can comprehensively capture the characteristics of tumor heterogeneity in images. At present, there are only two researches on the use of radiomics to predict VPI (36,37). Yuan *et al.* (36) analyzed the CT imaging characteristics of 327 cases of early lung adenocarcinoma with a maximum diameter ≤3 cm and found that several imaging characteristics (e.g., percentile 10%, WavEnLLS_2, and S-0_1SumAverage) reflected tumor heterogeneity and that differed significantly between the VPI positive and negative groups. The radiomics model predicted VPI with an accuracy of 90.5%, but the study included 72 lesions with no imaging contact with the pleura as the VPI-negative group. In addition, the radiomics model was constructed based on only the tumor and not the combined CT morphological features. Zha *et al.* (37) excluded the pure GGN type and included a total of 659 cases of IA lung adenocarcinoma. Based on the tumor imaging features and CT signs, a comprehensive prediction model of VPI was constructed, with an AUC value of 0.89 in the training set and 0.88 in the internal verification set. Although the above tumor-based imaging models had a good discriminative ability, these studies lacked external validation, and the universality and repeatability of the models require further evaluation. In recent years, peritumoral imaging features have reported better predictive efficacy in predicting lung adenocarcinoma invasiveness, lymph node metastasis, spread through air spaces, and vascular invasion. However, the prediction of VPI of lung cancer by peritumoral imaging has not been explored, thereby requiring further research into peritumoral information and its predictive value.

Radiomics studies were all retrospective studies, and there was a certain degree of bias in the selection of samples, a prospective multicenter study should improve the generalization ability and optimize the model. At present, the radiomics features were derived from the regions of interest (ROIs) mainly through manual segmentation, which was relatively time-consuming and laborious. Therefore, an automatic segmentation method with high repeatability and accuracy should be developed. It was difficult to explain the biological significance of some radiomics features. In the future, radiomics-genomics research can be carried out to improve the biological interpretability of radiomics models.

Deep learning

The rapid, detailed, and massive data processing capabilities of deep learning provide advanced engineering means for in-depth exploration of higher-dimensional image indicators and play a crucial role in the analysis and integration of various factors and the establishment and verification of prediction models. At present, there is only one study on the prediction of VPI based on the deep learning model. Choi *et al.* (38) established and verified the value of the CT-based deep learning model in predicting VPI in early lung cancer and compared it with the diagnostic efficiency of radiologists. In this retrospective study, dataset 1 (for training, tuning, and internal validation) included 676 patients with clinical stage IA lung adenocarcinomas resected between 2009 and 2015. Dataset 2 (for temporal validation) included 141 patients with clinical stage I adenocarcinomas resected between 2017 and 2018. Results reported that the AUC value of VPI predicted by this model was 0.75 [95% confidence interval (CI), 0.67–0.84]. Three radiologists predicted that the AUC values of VPI ranged from 0.73 to 0.79, and hence, the predictive power of the model was comparable to that of radiologists. However, the model had a higher standardized partial AUC, with a sensitivity of 93.8% and specificity of 31.2% for a high sensitivity cut-off value (0.245). The sensitivity of the high specificity cut-off value (0.448) was 47.9%, and the

specificity was 86.0%. The predictive efficacy of the deep learning model was comparable to that of radiologists, and high sensitivity and specificity can be regulated according to clinical needs. However, there were some limitations in this study. Firstly, the overall prediction efficiency of the deep learning model was low, and the information on traditional CT signs, clinical laboratory examination, and radiomics features was not integrated. Secondly, only internal time verification was evaluated. In future studies, a cross-modal 3D deep learning comprehensive model should be constructed and further verified on an independent external verification set to evaluate the universality of the model. Thirdly, EFs stain was not performed to assess VPI in dataset 1. As label noise is associated with the model performance, there was room to improve the model performance. Fourthly, the model was not fully automated, and it required manual tumor annotations. In the future, a larger sample size with accurate pathological VPI grading should be collected to establish the model. Deep learning models are widely used in clinical practice still require meticulous validation and demand specific software programs, experience, and time.

Conclusions

In conclusion, VPI is a prominent prognostic factor of lung cancer, and an accurate evaluation of VPI is of great significance for the selection of surgical and postoperative treatments. Recent studies have predicted VPI based on CT signs, ^{18}F-FDG PET/CT, and MR, but each prediction method has its advantages and limitations. With emerging technologies, radiomics and deep learning have great advantages in the field of diagnosis and are expected to become the core of precision medicine in the treatment of lung cancer. However, they have not been widely used to predict VPI in lung cancer. Hence, their accuracy and preoperative prediction mechanism require further exploration.

Acknowledgments

Funding: This research was funded by the National Key R&D Program of China (Nos. 2022YFC2010000 and 2022YFC2010002), the Key Program of National Natural Science Foundation of China (No. 81930049), the National Natural Science Foundation of China (Nos. 82171926 and 82202140), the Shanghai Sailing Program (No. 20YF1449000), the Shanghai Science and Technology Innovation Action Plan Program (No. 19411951300), the Clinical Innovative Project of Shanghai Changzheng Hospital (No. 2020YLCYJ-Y24), and the Program of Science and Technology Commission of Shanghai Municipality (No. 21DZ2202600).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1318/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1318/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1318/coif). The authors have no conflicts of interest to declare.

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

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Cite this article as: Wang Y, Lyu D, Fan L, Liu S. Research progress in predicting visceral pleural invasion of lung cancer: a narrative review. Transl Cancer Res 2024;13(1):462-470. doi: 10.21037/tcr-23-1318

