Review Article

Prediction of pleural invasion using different imaging tools in non-small cell lung cancer

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Contributions: (I) Conception and design: HC Liao, WM Lin; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Clinical staging of non-small cell lung cancer (NSCLC) is used for planning therapeutic strategies. In particular, pleural invasion is regarded as an indicator for upstaging to T2 or T3 in the current 8th TNM staging system; patients with pleural invasion should be indicated for lobectomy rather than sublobar resection. Therefore, accurate preoperative prediction of pleural invasion is important for surgical planning. In recent years, different radiological investigations for patients with NSCLC have been widely used, and methods for more precise detection have been developed in the current medical imaging studies. Therefore, several radiological investigation tools have been used for the prediction of pleural invasion. In this article, to identify the imaging modalities for accurate prediction of pleural invasion, we reviewed the different methods used for this purpose and discussed their advantages and limitations.

Keywords: Computed tomography (CT); non-small cell lung cancer (NSCLC); pleural invasion

Submitted Nov 09, 2018. Accepted for publication Jan 07, 2019.
doi: 10.21037/atm.2019.01.15
View this article at: http://dx.doi.org/10.21037/atm.2019.01.15

Introduction

Clinical staging of non-small cell lung cancer (NSCLC) is used for guiding therapeutic planning for the patient; therefore, accurate diagnosis and staging in the preoperative period is important. Several studies (1,2) have shown that visceral pleural invasion (VPI) is a poor prognostic factor in early stage NSCLC. According to these previous reports, pleural invasion of NSCLC has been adopted as a T impact factor in the TMN staging system of UICC since 1970s (3,4). Based on the 7th edition TNM staging of lung cancer, pleural invasion has been designated as PL0 (tumor does not invade beyond the elastic layer), PL1 (tumor invades beyond the elastic layer), PL2 (tumor invades the visceral pleural surface), and PL3 (tumor invades the parietal pleural) (5). PL0 is not defined as VPI. The TNM staging system defined PL1 and PL2 as VPI (staged as T2) and PL3 as parietal pleural invasion (staged as T3). Further, the latest 8th TNM staging has retained the same pleural invasion classification (6) (*Figures 1,2*).

The revised staging of NSCLC has a strong impact on the treatment strategies. For example, extrapleural dissection with en-bloc resection were recommended for parietal pleural invasion (7), and lobectomy instead of segmentectomy was recommended in patients with VPI (8). Therefore, noninvasiveness of early lung cancer should be precisely identified in preoperative radiological evaluations, as limited sublobar resection surgery (segmentectomy or

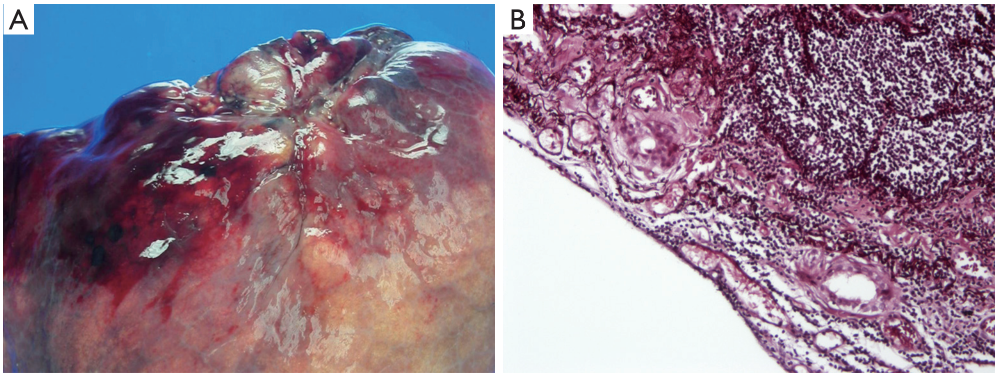

Figure 1 Illustration of PL1 pleural invasion. (A) Gross appearance of PL1 pleural invasion; (B) tumor invades beyond the elastic layer but is not exposed on the visceral pleural surface, which can be confirmed by elastic stain.

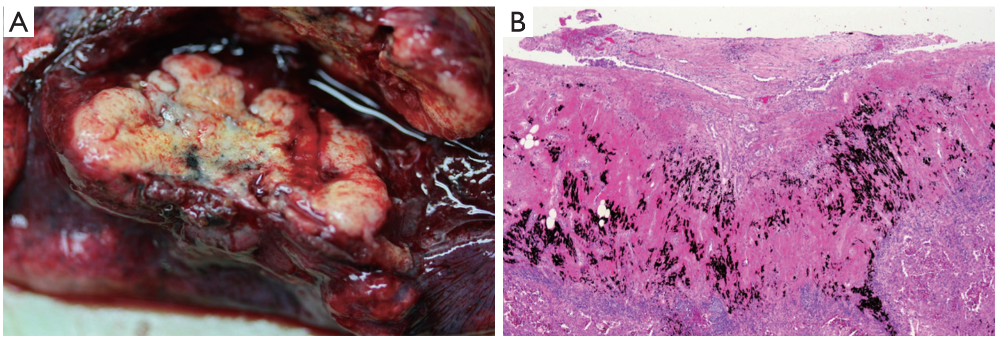

Figure 2 Illustration of PL2 pleural invasion. (A) Gross appearance of PL2 pleural invasion; (B) visceral pleural surface invasion by peripheral cancer cells after disruption of mesothelial cells and seeding of the pleural surface.

wedge resection) is indicated in such cases.

Chest radiography (CXR) is the most common tool for the initial investigation of lung disease. However, CXR is not suitable for assessing pleural invasion in early stage NSCLC. Ultrasound (US) (9,10), computed tomography (CT) (11-21), magnetic resonance imaging (MRI) (22,23) and fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) (24-26) have been used for preoperative prediction of pleural invasion. However, no single imaging method has been proposed for the definitive diagnosis of pleural invasion, and each imaging modality has its advantages as well as limitations (*Figure 3*). These imaging tools have the potential to facilitate better clinical decision-making, particularly in the treatment of patients with cancer (27). Therefore, to identify the appropriate imaging modality for this purpose, we aimed to review the imaging methods indicated in published reports for predicting pleural invasion of NSCLC.

Ultrasonography

US is a non-invasive, widely accessible, and low-cost tool used for medical imaging. It has been used for evaluation of chest wall invasion (PL3) (9). If the mass is observed to be attached to the pleura, with loss of movement during respiration under US examination, chest wall invasion should be highly suspected. A prospective study that included 90 patients revealed that, compared to CT scan examination (sensitivity, 42%; specificity, 100%) (10), US has better sensitivity (89%) and specificity (95%) for assessing chest wall involvement by a lung tumor.

Preoperative prediction of pleural invasion by US has some limitations. First, the accuracy of intraoperative US is highly dependent on the skill and experience of the operator. Second, it is difficult to predict VPI (PL1 and PL2) by using US; this is because VPI does not involve the chest wall and does not affect pleural movement during

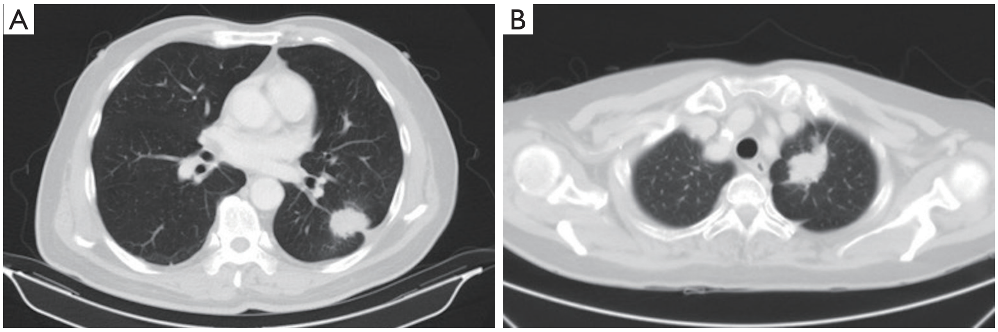

Figure 3 Illustrations showed the difficulty of preoperative prediction of visceral pleural invasion in lung cancer patients. (A) The preoperative CT scan reported a left upper lobe lung tumor with pleural retraction and suspicious pleural invasion. Post-operative orcein staining confirmed penetration of the elastic layer of the visceral pleura (PL1); (B) the preoperative CT scan revealed a spiculated enhancing tumor at the left apical lung with pleural tags. However, the post-operative pathologic report showed that the tumor did not invade the visceral pleura (PL0), as revealed by orcein staining. CT, computed tomography.

respiration. Currently, reports on predicting VPI using US are lacking.

CT

Prediction of chest wall invasion

Chest CT and bone scan are usually used for preoperative evaluation of the depth of chest wall invasion. According to pathological findings, invasion of only the parietal pleura is defined as shallow invasion, and invasion of the soft tissue or ribs is defined as deep invasion.

Kawaguchi *et al.* (11) retrospectively surveyed 132 patients who had undergone resection for NSCLC involving the chest wall, and they showed that tumor invasion beyond the parietal pleura on the preoperative CT [hazard ratio (HR) =6.824, P=0.005] and complaints of chest pain (HR =3.282, P=0.015) were independent indicators of deep invasion into the chest wall. En-bloc resection was recommended in patients with chest pain and/or deep invasion on chest CT.

Tumor disappearance ratio (TDR)

The pure ground grass opacity component of the lung on CT is typically believed to indicate non-invasive or precancerous lesions. In contrast, the solid component has been recognized to indicate invasive lesions. Evaluation of the TDR is one of the methods used to evaluate the proportion of tumor in order to predict tumor invasiveness (12-14). TDR is defined as 1-DM/DL (DM: maximum tumor dimension on mediastinal window, DL: maximum tumor dimension on lung window). Tumor size is evaluated using both the mediastinal window setting and lung window setting; evaluation of tumor size using this setting is considered to have greater prognostic value than that that only using the lung window setting.

Some studies used TDR to predict pathologically noninvasive (without vessel invasion, pleural invasion, and lymph node metastasis) NSCLC. Shimada *et al.* (12) analyzed 363 patients and showed that the combination of a TDR larger than 0.5 and the absence of spiculation was highly predictive of noninvasive or minimally invasive T1aN0M0 peripheral NSCLC (P<0.001). However, TDR may be used to indicate only tumor invasiveness; it could not predict pleural invasion precisely.

Consolidation-to-tumor ratio (CTR)

CTR is another method for analyzing whether radiologic density of tumor could be regarded as a predictor of tumor aggressiveness. CTR is defined as the ratio of the maximum consolidation diameter (C) to maximum tumor diameter (T) on lung window (15-17). It has been used to predict the risk of pleural invasion indirectly by predicting the extent of tumor aggressiveness.

Suzuki *et al.* (15) reported that CTR on lung window [window level = −500 to −700 Hounsfield unit (HU), window width =1,000 to 2,000 HU] could be used to predict pathologically noninvasive (without nodal involvement, vascular invasion, or lymphatic invasion) lung cancer, and

CTR less than 0.25 was considered to indicate radiological noninvasiveness in T1N0M0 (tumor size less than 2 cm) NSCLC (sensitivity: 16.2%, specificity: 98.7%). Similar to TDR, CTR may also be indicated for predicting only tumor invasiveness; it could not predict pleural invasion precisely.

Tumor border analysis

Although CT is widely used for staging NSCLC, its ability to predict pleural invasion is still limited. A tumor abutting the pleural surface does not indicate invasion. Many methods for predicting pleural invasion using CT have been published (18-21), one of which is analysis of the tumor border.

Some radiologists diagnosed pleural invasion of NSCLC by using conventional CT criteria combined with at least two of the following three criteria: tumor size more than 3 cm, with contact with the neighboring pleura; obtuse angle with the contact surface; and related pleural thickening. Two expert radiologists using conventional criteria showed that the sensitivity and specificity rates were 46.7% and 74.2%, and 91.3% and 84.8%, respectively (18).

Another method used to predict pleural invasion was the measurement of the ratio of the arch distance (interface between the tumor and surrounding structures) to the maximum diameter of the tumor (19). For this ratio, a value more than 0.9 indicated an accurate diagnosis of chest wall invasion (PL3) (sensitivity and specificity for thoracic invasion, 89.7% and 96.0%).

In addition, pleural tags were also mentioned and were defined as one or more linear strands that extend from the tumor surface to the pleural surface. A retrospective study (20) classified pleural tags on CT into 3 types (type 1, one or more linear pleural tag; type 2, one or more linear pleural tag with a soft tissue component at the pleural end; and type 3, one or more soft tissue cord-like pleural tag); type 2 pleural tag has the statistical significance on the prediction of the VPI by NSCLC that is not abutting the pleura [positive likelihood ratio (LR): 5.06; accuracy: 71%; sensitivity: 36.4%; specificity: 92.8%, P<0.001].

Hsu *et al.* (21) evaluated the tumor border for predicting plural invasion in peripheral NSCLC in 136 patients. A retrospective study was performed and the tumor border was classified into 5 types. The type 5 tumor border (convex border with perpendicular or blunt angle) has a high positive predictive value (PPV) and specificity for predicting pleural invasion of peripheral NSCLC (LR: 5.20; accuracy; 57%; sensitivity: 45%; specificity: 91%; PPV: 94%; and negative predictive value: 36%). They also reported that a blunt angle, pleural contact >3 cm, and pleural thickening are not significantly different in patients with and without pleural invasion.

MRI

The basic principle of using MRI to evaluate pleural invasion is similar to that for the use of US. Physicians may use respiratory dynamic MRI to assess the movement of a tumor abutting the chest wall during breathing; tumors without parietal pleura invasion are expected to show movement with each breath. Akata *et al.* (22) reported that respiratory dynamic MRI improved the accuracy for predicting chest wall invasion of NSCLC (sensitivity: 100%, specificity: 82.9%).

Dynamic MRI is a dynamic evaluation, similar to US, for chest wall invasion. However, these dynamic evaluations could not distinguish between invasion and adhesion, and it should be exclusively used for the prediction of parietal pleura invasion or chest wall invasion. Another similar and practical method for evaluation of parietal pleura invasion is the dynamic CT scan. The advanced technology makes CT scans much faster and more precise than before. It can provide precise information on the movement of a tumor and nearby organs. The speed and spatial resolution of the 320-slice CT make it a useful and non-invasive tool for the initial evaluation of cardiac disease. Choong *et al.* (23) tried to use 320-slice CT for detecting invasion of lung tumors into the adjacent structures and termed as dynamic four-dimensional CT (4D CT); eight cases of NSCLC were evaluated. They revealed that this modality may be useful in the preoperative assessment of invasion into adjacent structures. However, few reports have been published on the use of 4D CT for pleural invasion.

PET

PET is an important tool for staging of cancer. It is usually used to assess metastasis and localize mediastinal nodal involvement (24,25) in patients with suspected cancer. However, it is difficult to assess pleural invasion by PET directly. Generally, ^{18}F-FDG uptake is highly correlated with tumor invasiveness. The higher is the ^{18}F-FDG uptake, the higher are the proliferation and invasion exhibited by tumors. Therefore, ^{18}F-FDG PET/CT was used for predicting VPI according to the SUVmax. Tanaka *et al.* (26) used SUV_{max} 4.3 on ^{18}F-FDG PET/CT as the cutoff value for predicting VPI in lung adenocarcinoma with pleural contact. In their study, 208 patients were analyzed, and 85% accuracy was observed. In contrast, no case with SUV_{max} <1.3 showed pleural invasion (any tumor size). Therefore, pleural contact with high SUV may be a predictive factor for pathological VPI in lung adenocarcinoma.

Conclusions

Among CXR, US, PET scan, CT scan, and MRI, CXR remains the modality of choice for the initial investigation of patients with suspected pleural disease, such as mesothelioma or pleural effusion. US is useful for monitoring pleural changes, but the accuracy of US for detecting VPI in NSCLC is not advocated. PET and PET/CT is useful for the differentiation of malignant and benign pleural lesions and effusions. Further, CT scan is best understood by appreciating the different morphology in pleura, especially in patients with small tumor size.

In future, we believe there will be more technical challenges in the process of radiomic analysis, and will be more clinical applications for radiomic analysis in lung cancer image researches (27-29). These novel techniques may provide more precise information for preoperative prediction of pleural invasion and may improve the diagnostic accuracy and clinical outcomes in patients with lung cancer.

Acknowledgements

Funding: This study was funded by the National Taiwan University Hospital, Taipei, Taiwan (NTUH107-N004038, MS-419), and the Ministry of Science and Technology, Taiwan (MOST 107-2221-E-002-080-MY3).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Bai JH, Hsieh MS, Liao HC, Lin MW, Chen JS. Prediction of pleural invasion using different imaging tools in non-small cell lung cancer. Ann Transl Med 2019;7(2):33. doi: 10.21037/atm.2019.01.15