Editorial Commentary

Visceral pleural invasion: predictable on CT?

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The visceral pleura consists of a single layer of mesothelial cells resting on a basement membrane, a submesothelial connective tissue layer, a layer of elastic fibers and a connective tissue layer that separates the elastic layer from the lung parenchyma which is demarcated by a layer of pneumocytes resting on a thin basement membrane (1). A tumor within the subpleural lung parenchyma or a tumor that superficially invades into the connective tissue beneath the elastic layers without penetrating it, is defined as PL0. A tumor is categorized as PL1 when it invades beyond the thick elastic layer of the visceral pleura. Tumor invasion to the visceral pleural surface is PL2 and invasion of any component of the parietal pleura is PL3 (1). Gross examination of the lung cancer resection specimen should guide histologic sampling of the pleura with greatest concern for invasion. Use of elastic stains is recommended to be used in cases where differentiating PL0 from PL1 status is difficult based on review of hematoxylin eosin stains alone (2,3). It is also recommended for these cases where visceral and parietal pleura are adherent. For being classified as PL1, tumors need to cross beyond the thick elastic layer within the visceral pleura (1).

For the past several decades, visceral pleural invasion (VPI) is recognized as an independent negative prognostic factor, with increased risk of locoregional recurrence and systematic metastases, including intralobar N1 nodal recurrence. A systematic review and meta-analysis by Jiang *et al.* investigated the impact of visceral pleural invasion in node-negative non-small cell lung cancer in thirteen relevant studies involving 27,171 patients. Frequency of VPI in the studies examined, was 21% (mainly adenocarcinomas) and was related to the predominant peripheral location of these tumors. The authors showed that VPI was a significant adverse prognostic factor with reduced overall survival, including patients with tumor size ≤3 cm (OR, 0.71; 95% CI, 0.64–0.79; P<0.001) (4). These findings are in line with those of the International Association for the Study of Lung Cancer database: VPI was found to confer a worse prognosis (multivariate analysis, hazard radio 1.51; 95% CI, 1.39–1.63; P<0.001) (5). Dziedzic *et al.* investigated the risk factors for local and distant recurrence after surgical treatment for NSCLC in a group of 14,578 patients. In their cohort, 6.3% (917/14,578) of patients showed VPI. In the group of patients with recurrence, 16% (450/2,816) showed VPI, whereas in the group of patients without recurrence, VPI was present in only 4.4% (521/11,762). Multivariate analysis indicated an independent effect of visceral pleural invasion (HR, 1.641; 95% CI, 1.21–2.22) (6).

Kudo *et al.* showed that VPI was significantly associated with more extensive hilar or mediastinal lymph node involvement. They hypothesized that the visceral pleural is very rich in lymphatic vessels, with an intercommunicating network arranged over the lung surface that penetrates into the lung parenchyma to join the bronchial lymph vessels with drainage to various hilar lymph nodes (7). Lung cancers in a subpleural location can disseminate cancer cells throughout the pleural cavity, with subsequent systematic dissemination through subpleural lymphatics connecting with the pleural space (7). These mechanisms are hypothesis based on physical movement of malignant cells, rather than

established facts with the process of metastasizing being far more complex (8,9).

There are significant differences between PL-status with PL1 and PL2 being worse than PL0 and PL2 even having a worse prognosis than PL1 (5). VPI has been incorporated in the 8th edition of the TNM Classification for lung cancer. Tumors are upstaged in relation to their relationship with the pleura. VPI in a tumor of less than 3 cm is upstaged from T1 to T2 (5,10,11). Although at clinical staging VPI can be assumed by some imaging features, it is emphasized by Rami-Porta *et al.* that VPI is a pathological descriptor (5).

Non-invasive image-based tumor staging, including assessment of the VPI, has been of interest to radiologists and previously investigated in numerous studies (12). The imaging feature of pleural retraction definitely has its role in assessing the likelihood of malignancy in solitary pulmonary nodules (13,14), but the ability of CT to predict pleural invasion is limited.

Pleural tags are defined as one or more linear strands that extend from the nodule surface to the pleural surface. They correlate on histopathology with thickened interlobular septa from localized edema, tumor extension within or outside lymphatic vessels, inflammatory cells or fibrosis. Hsu *et al.* retrospectively investigated in 141 patients the association of pleural tags with visceral pleural invasion of NSCLC that does not abut the pleural surface in. They showed that type 2 pleural tags—defined as one or more linear pleural tags with soft-tissue component at the pleural end on mediastinal window images—provided moderate evidence to rule in visceral pleural invasion by NSCLC that did not abut the pleura (with 70.8% accuracy, sensitivity 36.4%, specificity 92.8%, PPV 76.2%, NPV 69.6%) (15). This feature cannot be used to differentiate PL1 from PL2.

In a retrospective study by Yang *et al.* nine types of pleural signs in 52 adenocarcinoma pulmonary nodules were investigated. They included five types of non-interlobar fissure pleura and four types of interlobar fissure pleura (16), based on the presence or absence of linear pleural tags, associated soft tissue component at the pleural end and pleural shift. They showed that one or more bold-wire pleural tags with soft tissue components at the pleural end (for non-interlobar fissure pleura) and a tumor that pushes the pleura (for interlobar fissure pleura) were most associated with VPI. One or more linear pleural tags without pleural thickening (for non-interlobar fissure pleura) was associated with absence of VPI. Zhao *et al.* retrospectively investigated 156 pulmonary nodules with ground glass morphology. They showed that incidence of VPI was significantly higher in part-solid nodules (32.2%) compared to pure ground-glass nodules (17.4%). Nodule abutment or a pleural tag was not reliable to predict or exclude VPI in peripheral subsolid nodules with VPI (all PL1) only present in 25.6% (47/156) of these cases (17). Ahn *et al.* showed in 188 peripheral pulmonary nodules (adenocarcinoma) that a part-solid morphology, CT features of pleural contact, pleural thickening, a solid proportion greater than 50% and nodule size >2 cm were shown to be significant indicators of VPI with specificity of 99.2% when all variables were used in combination (18). In contrast to pleural tags, pleural signs and pleural thickening as investigated by different authors, Imai *et al.* developed a simple non-invasive technique for evaluating pleural invasion on routine CT by measuring the arch distance to maximum tumor diameter ratios (19). A cut-off ratio of 0.9 best distinguished between PL3 tumors and those of the other two groups (PL1 and PL2).

Recently, Kim *et al.* published a paper 'CT-defined Visceral Pleural Invasion in T1 Lung Adenocarcinoma: Lack of Relationship to Disease-Free Survival' in *Radiology* (20). The purpose of their study was to validate the diagnostic accuracy and to analyze the prognostic value of CT findings for the prediction of pathologic VPI (pVPI) in patients with resected node-negative lung adenocarcinomas. Their study population comprised of 695 patients with adenocarcinoma presented as solid or part-solid nodules, with exclusion of pure ground glass nodules and other histological subtypes of cancer. Based on the available evidence in literature, the authors used the combination of CT-imaging features for categorizing nodules in 4 groups. Group 1 (CT VPI1) consisted of nodules with a contact length greater than one-fourth of the tumor circumference. Group 2 (CT VPI2) were lesions group 1 (CT VPI1) or with pleural retraction, Group 3 (CT VPI3) were lesions group CT VPI1 or pleural tags with thickening at the pleural end. The last group, Group 4 (CT VPI4) were lesions group CT VPI1, pleural retraction or pleural tags with thickening at the pleural end (20). Diagnostic accuracies of CT VPI ranged from 63.7% to 72.3%. Positive predictive values were low, ranging from 44.1% to 56.4%: about half of the CT-based pVPI predictions were false positive. If CT-features would be used to evaluate VPI for staging, at least 50% of patients would have falsely been upstaged as T2. Negative predictive values ranged from 76.9% to 87.2%. When looking into the value of CT VPI and pVPI for prediction of disease-free survival (DFS) with a multivariable model, none of the CT VPI combinations were statistically significant, with hazard

ratios of 1.40 (CT VPI1), 1.48 (CT VPI2), 1.06 (CT CPI3) and 1.21 (CT VPI4). The multivariable model did however show that age and clinical T category were significant predictors of DFS.

In regard to the study design, some limitations should be mentioned. From a pathological point of view, differentiation between PL0, PL1 or PL2 was based on the hematoxylin-eosin-stained slice whereas elastin stains are preferred. From a radiological point of view, it is known that visual assessment of nodules is prone to variability (both intra- and interobserver) regarding categorization of nodules in solid versus subsolid as well as measurement of the solid component in subsolid nodules (21).

The conclusion of the study by Kim *et al*. is that diagnostic CT features for pathologic visceral pleural invasion are not independent prognostic factors in clinical T1 lung adenocarcinomas. Currently there is not enough evidence that lung cancers that present on CT with close contact to the pleura or with pleural tags, can be upstaged T1 to T2.

Radiologic-pathologic correlation remains challenging and incorporation of (CT-)imaging findings in staging systems currently is not a valid option. In an era where artificial intelligence is reshaping the imaging world, one might expect that in the future validated deep-learning algorithms will find their way and claim their role in integrating imaging features into staging systems.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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