Editorial

A conundrum of honeycombing: challenges in tumor size estimation in patients with honeycombing in the lung

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Comment on: Ishizawa H, Matsuda Y, Ohno Y, *et al.* Honeycomb lung is a major risk factor for preoperative radiological tumor size underestimation in patients with primary lung cancer. J Thorac Dis 2023;15:516-28.

Keywords: Honeycombing; interstitial lung disease (ILD); interstitial lung diseases (ILDs)

Submitted Mar 16, 2024. Accepted for publication Mar 28, 2024. Published online May 27, 2024.
doi: 10.21037/jtd-24-437
View this article at: https://dx.doi.org/10.21037/jtd-24-437

Interstitial lung diseases (ILDs) are a heterogeneous group of lung disorders characterized by inflammation and/or fibrosis. ILD represents a diverse group of over 200 lung diseases of varying etiologies (1-3). Idiopathic pulmonary fibrosis (IPF) is the most common ILD characterized by a usual interstitial pneumonia (UIP) pattern on imaging and histology (1). Patients with IPF are typically male with an active or former smoking history. IPF is one form of idiopathic interstitial pneumonia (IIP) (3). Other forms of IIP include nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), and lymphocytic interstitial pneumonia (LIP), among others (3). ILDs can also be secondary to connective tissue disease, occupational, drug-induced, and antigen-associated hypersensitivity pneumonitis (1).

Lung cancer is a common comorbidity in ILD (4-6). A recent systematic review and meta-analysis found an increased risk of lung cancer in patients with IPF even after adjustment for age, smoking, and sex (4). In patients with IPF, reported lung cancer prevalence ranges from 3% to 48% (4-7). It is difficult to determine the true incidence and prevalence of lung cancer in patients with ILD due to confounding factors in many of the reported studies. The cancer typically presents as peripheral lesions, mostly in the inferior pulmonary lobes, either close to or within the ILD areas (5-7). Hence, it is quite likely that the presence of fibrosis on chest imaging can influence tumor size estimation, which is pivotal to clinical decision-making, thus significantly impacting cancer care and prognosis in ILD. One study published in 2016 demonstrated a greater frequency of preoperative tumor size underestimation of 10 mm in IIPs than without IIPs (8). The authors attributed this underestimation to the tumor spread in regions of honeycomb lung (8).

The high prevalence of lung cancer in ILD is likely related to many shared risk factors among both conditions (4-7). Smoking is a well-recognized risk factor for both lung cancer and ILD, in particular for IPF. Other potential shared risks include genetics, environmental exposures, and immune system dysfunction (9). Mechanical forces in the fibrotic regions of the lung have also been proposed as a novel risk factor for cancer development in ILD (9). It is hypothesized that these mechanical forces arising from the fibrotic areas may impact cell regulation and proliferation leading to cancerogenesis (9). It is possible this is exacerbated in areas with more significant architectural distortion including regions with honeycombing. However, there is a lack of studies on lung cancer and tumor

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Table 1 Tumor size underestimation of >10 mm on pre-operative CT chest based on radiographic features present

Study	Normal	Honey combing or UIP	Reticulation present or possible UIP	Emphysema or inconsistent with UIP
Ishizawa *et al.* 2023, (15)	47/628 (7.5%)	5/15 (33.3%)	2/30 (6.7%)	15/207 (7.2%)
Fukui *et al.* 2016, (8)	NA/1,085 (NA)	5/21 (23.8%)	2/35 (5.7%)	7/80 (8.8%)

CT, computed tomography; UIP, usual interstitial pneumonia; NA, not applicable.

infiltration in regions of honeycombing.

The gold standard therapeutic option for early-stage non-small cell lung cancer (NSCLC) is surgical resection with lymph node dissection. However, surgical resection is challenging in patients with underlying ILD due to a higher risk of morbidity and mortality compared to patients without ILD (5,6,10,11). Alternative treatments like stereotactic radiotherapy or radiofrequency ablation may be considered for ILD patients who are unfit for surgery, but these options also carry risks of acute exacerbation and pneumonitis (12-14). Similarly, many chemotherapy agents are associated with pulmonary toxicity, exacerbating underlying ILD or causing new-onset ILD in the form of drug-induced pneumonitis (12-14). Consequently, all therapeutic options pose increased risks of disease progression and mortality in ILD patients, whose prognosis is often poor even at the initiation of treatment (11). Given these considerations, accurate tumor size identification becomes paramount to effectively selecting therapies that balance benefits and risks.

The study conducted by Ishizawa and his colleagues' sheds light on the challenges faced in accurately determining the size of tumors in lung cancer patients with underlying ILD. They recruited patients diagnosed with lung cancer between January 2015 and June 2020, at Fujita Health University, a tertiary care center (15). The cohort was divided into those with normal lungs (n=628, 71.1%), emphysema (n=207, 23.4%), reticulations (n=30, 3.4%) and honeycombing (n=15, 1.7%) as seen on computed tomography (CT) chest, and radiological tumor size estimates were compared with pathologic/histologic measurements (15). The authors used the 7th edition of tumor, node, metastasis (TNM) lung cancer staging of tumor size estimation and staging the cancers (15). Their study revealed critical findings concerning the preoperative radiological assessment of tumor size in lung cancer patients compared to the size of the tumor evaluated by pathologic examination. It identified a significant risk of underestimating tumor size by 10 mm or more when honeycombing was adjacent to the tumor, as opposed to cases with reticulation, emphysema, or normal lung (P=0.003). Furthermore, the research highlighted a higher likelihood of tumor size underestimation in larger lesions (P=0.001) (15). Interestingly, there was no significant difference in tumor size underestimation between lung adenocarcinoma and squamous cell carcinoma (15). These findings raise substantial clinical concerns as they suggest that tumors near honeycombing areas may not be accurately evaluated in radiological assessments using current methodology, potentially leading to erroneous treatment decisions based on underestimated tumor dimensions.

While evaluating tumor size in areas of honeycombing holds significant clinical importance, this aspect remains inadequately addressed in current literature. The study conducted by Ishizawa and his colleagues makes a significant contribution in this regard. To the best of our knowledge, only one other study has investigated this issue, yielding similar results. *Table 1* provides a summary of the findings from these two studies (8,15).

Tumor size estimates are crucial, especially in small lesions, as they may determine the extent of the required surgical procedure. Lee and Altorki, along with the Lung Cancer Study Group, examined the outcomes of several studies comparing sublobar resections to lobectomy in treating early-stage NSCLC (16). Their findings indicate that sublobar resections, such as wedge resection or segmentectomy, are viable options for peripheral T1N0 NSCLC tumors measuring 2.0 cm or smaller, while lobectomies are preferred for larger tumors (16). Optimal therapeutic strategies are particularly crucial for patients with ILD to avoid subsequent surgical or non-surgical interventions (4-6). Indeed, inaccuracies in tumor size estimation may lead to inadequate sublobar resections, increasing the risk of recurrence and the need for further therapy (17-21). In extreme cases, these errors may even misclassify intermediate-stage tumors as early or advanced-stage as intermediate, potentially subjecting patients to unnecessary treatments that offer limited survival benefits and may worsen lung function (17-21). These consequences are especially concerning for ILD patients, given their

compromised lung function and poor performance status at baseline.

As mentioned earlier, Ishizawa and colleagues' research focuses on comparing honeycomb lung with reticulation, emphysema, and normal lung tissue (15). These comparisons offer a practical approach to contrasting chronic lung conditions with radiologically normal appearing lungs. Reticulation and emphysema are finer processes, while honeycomb lung often presents with significant architectural distortion, making it considerably more challenging to accurately interpret changes in CT images. Additionally, the use of thicker collimation, often up to 5 mm, in many oncologic CT studies may exacerbate the challenges in such scenarios. This could be at the root of tumor size underestimation with imaging (15).

One intriguing aspect noted in the study is the authors' choice to use the 7th edition of TNM in Lung Cancer from the International Association for the Study of Lung Cancer (IASLC) rather than the more recent 8th edition. While the newer edition refines the thresholds for smaller tumors, which could contribute to further tumor size underestimation, it also introduces a different approach to assessing tumor invasion pathologically (17-21). Specifically, the 8th edition no longer considers the lepidic architectural pattern as an invasive component when determining tumor size (17-21). This change is based on observations of lower recurrence rates in tumors with a predominant lepidic pattern (17-21). Consequently, the American Joint Committee on Cancer (AJCC) recommends that, for adenocarcinomas with a lepidic pattern, only the size of the invasive component (i.e., other patterns) should be considered to assign the T category (21). This shift in classification may have further implications for tumor size underestimation, particularly if some of the measured tumors in the study contained extensive lepidic architecture. The impact of using the 7th edition on the study results is unknown.

In conclusion, Ishizawa *et al.* provide valuable insights into the challenge of tumor size estimation in patients with ILD. Lung cancer decision-making hinges on accurate estimates of tumor size to guide appropriate interventions. Patients with ILD often face significant challenges when considering cancer resection surgery due to declining lung function and are at an increased risk of complications from other standard treatments including chemotherapy, immunotherapy, and radiation. This study underscores the importance of tumor size underestimation, particularly within the context of background fibrosis on chest imaging, a factor that disproportionately affects patients with ILD.

Moving forward, future studies should consider evaluating tumor size underestimation using the current 8th edition of TNM lung cancer staging and thinner CT axial slices, as this approach may yield more accurate results. Moreover, there is a pressing need to standardize the application of ILD protocols for high-resolution CT (HRCT) in cases involving pulmonary fibrosis and lung cancer. Such standardization could facilitate more accurate comparisons of ILD and cancer progression, particularly within oncology centers, ultimately improving patient care and outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-437/coif). S.V. reports honoraria from Boehringer Ingelheim. M.K. reports grants, consulting fees and lecture honorarium from Boehringer-Ingelheim. The other 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: Vahidy S, Pereira R, Martins-Filho SN, Kalluri M. A conundrum of honeycombing: challenges in tumor size estimation in patients with honeycombing in the lung. J Thorac Dis 2024;16(5):2709-2712. doi: 10.21037/jtd-24-437