EDITORIAL

Prognostic Impact of Ground-Glass Opacity/ Lepidic Component in Pulmonary Adenocarcinoma: A Hazy Staging Dilemma

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One of the most significant modifications that emerged from the eighth edition of TNM in the staging of pulmonary adenocarcinoma (ADC) was the introduction of the concept that only invasive size should be used for the size T-descriptor in part-lepidic nonmucinous ADCs. According to the 2011 International Association for the Study of Lung Cancer, American Thoracic Society/European Respiratory Society, and 2015 WHO lung adenocarcinoma classifications, the lepidic pattern is now regarded as a noninvasive growth pattern.[1] The clinical significance of this concept was supported by multiple studies reporting better stratification of these patients when using only the invasive size versus the total size.[2–6] By chest computed tomography (CT) scan, a lepidic architecture by histology generally corresponds to a ground-glass opacity (GGO), whereas the invasive pattern by histology corresponds to solid components by CT.[7] Therefore, from the point of view of radiology, only the size of the solid component in a part-solid nodule (PSN) impacts the clinical T-descriptor and not the GGO component. However, over the past few years, it has been suggested that the presence of a GGO component in radiology or a lepidic component in pulmonary ADC pathology could represent an independent predictor of good prognosis, regardless of the invasive features of the lesion. In some recent studies, PSNs were found to have a better prognosis compared with a solid ADC after stratification on the basis of the invasive size.[8–12] It has also been recently proposed that the GGO (G) or the lepidic (L) component be used as an additional prefix to the current T-descriptor.[10,11,13] However, the implementation of this proposition in the next edition of the TNM staging remains the subject of debate.

In this issue of the journal, Okubo et al.[14] aimed to further address this topic by evaluating the prognostic impact of the lepidic pattern in pulmonary ADC. The authors included 380 cases of surgically resected early-stage ADC (clinical stage IA) and categorized the tumors into lepidic-positive (any lepidic pattern present) and lepidic-negative tumors. Of note, pure lepidic lesions (pTis) and minimally invasive (MIA) ADC (pTmi) were excluded from the analyses, and cases with a positive surgical margin. The radiologic features of the lesions were also recorded including the total and solid tumor sizes and the GGO ratio.

Whereas recurrence-free survival (RFS) was improved in the lepidic-positive group, the presence of this pattern was not an independent prognostic factor in the multivariate model (hazard ratio = 046, 95% confidence interval: 0.19–1.13, $p = 0.09$). However, the discrepancy between the hazard coefficient obtained from the univariate and multivariate analyses was relatively small, which is relevant because multivariate models are inherently more stringent. This is especially true given the small sample size of some of the groups. The investigators also failed to exhibit a prognostic effect for the extent of the lepidic component in PSN, although when a lepidic ratio of more than 0.1 was used in the multivariate model, the p value was marginally above the level of significance ($p = 0.05$). Of note, this observation was also supported by the finding that a GGO ratio greater than 0.1 was significantly associated with a better prognosis in the multivariate analyses (hazard ratio = 0.30, 95% confidence interval: 0.12–0.81, $p = 0.02$).

Overall, this study presents significant methodological strengths. First, both radiologic GGO and pathologic

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lepidic components were assessed by two radiologists and two pathologists under blind conditions, which minimizes the associated evaluation biases. Second, the primary outcome used for the study was the RFS rather than the overall survival, which better reflects the clinical evolution of surgically removed early-stage lung ADC. Third, the authors excluded in situ and MIA ADCs. These two subtypes exhibit 100% RFS when completely resected, and hence, would have skewed the lepidic-positive group toward a better outcome. Finally, given the strong univariate association between several variables evaluated (solid and invasive size, invasive histologic patterns, etc.), multivariate analyses were carried out as part of the statistical design.

Nevertheless, there are a few caveats that warrant further consideration. As mentioned by the authors, the most important limitation is the relatively low number of patients in each of the stage I subcategories and the low number of events inherent to the good prognosis associated with clinical stage I resected disease limiting the number of variables included in the multivariate model, reducing the overall statistical power. This limitation most likely explains why well-known predictors of prognosis, such as solid size in radiology and invasive size in pathology, were not statistically significant when included in a multivariate model ($p = 0.13$ and $p = 0.16$, respectively). In addition, the inclusion of invasive mucinous ADC (n = 24) in this study raises some concerns. Indeed, the clinical behavior, the prognosis impact of architecture patterns, and the radiologic features of invasive mucinous ADC are different from those of nonmucinous ADC and may have influenced the overall results.

The interesting findings by Okubo et al.[14] shed new light on the topic of GGO/lepidic pulmonary ADC and prognosis. Although the findings are somewhat consistent with previous reports that found no prognostic impact of lepidic pattern/GGO component,[12,15,16] there are also recent data suggesting that the presence of a GGO component identified by CT in resected early-stage ADC is an independent indicator of a good prognosis. However, one must keep in mind that some of these studies included varying histologies such as non-ADCs and in situ and MIA, which may have impacted the results.[8–11,17] Another interesting finding highlighted by the group was that they found a weak correlation between the GGO and the lepidic ratios. This might be explained by the fact that GGO features identified by CT can sometimes be seen in tumors with nonlepidic patterns, whereas some lepidic ADCs can exhibit solid patterns identified by CT.

In conclusion, the prognostic impact of the GGO component in early-stage cancers has become particularly relevant given the wide implementation of lung cancer screening programs across the globe and the increased detection of early-stage disease. Although there is a growing body of literature suggesting an independent prognostic effect of the GGO/lepidic component, there may be study design issues affecting the results. The study published by Okubo et al.[14] reminds us that some caution is warranted before advocating for the addition of a new GGO/lepidic element to the T-descriptor in the actual staging system. In particular, before moving forward with this concept, the impact of the lepidic component should be validated at different institutions across the world to account for differences in tumor epidemiology, biology, and pathology. In addition, standardization of experimental designs that include adequate sample size to perform multivariate analyses, cohorts only composed of nonmucinous ADC, and a precise definition of GGO and lepidic components will also help investigators draw definitive conclusions. In addition, one must keep in mind that adding an extra descriptor to the TNM staging creates an additional layer of complexity, which makes it more challenging to implement on a global scale.

CRediT Authorship Contribution Statement

Philippe Joubert: Writing - original draft, Manuscript submission, Revision.

William D. Travis: Writing - review and editing.

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