Editorial

Complex glandular pattern as an independent predictor of survival probability in lung adenocarcinoma

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Approximately one year ago, a new grading system for invasive pulmonary adenocarcinoma was proposed from the International Association for the Study of Lung Cancer (IASLC) pathology committee (1). The new system is based on a three-graded model starting with lepidic predominant tumors (grade 1), continuing with acinar or papillar predominant tumors (grade 2) and ending with poorly differentiated tumors with high-grade patterns exceeding 20%. The high-grade patterns consist of solid tumors, micropapillary tumors and complex glandular pattern (CGP) tumors (grade 3). Since the new system takes multiple high-grade patterns into account for the same cutoff, it is unclear to which extent CGP tumors contribute to the prognosis of poorly differentiated tumors. CGP tumors represent tumors with a cribriform pattern or a fused gland pattern. Cribriform pattern is characteristic of a punctuated appearance while fused gland pattern is characteristic of multiple glands that are not separated by any stroma (2).

In the study by Bai and colleagues, the prognostic role of CGP is evaluated as an independent predictor from solid tumor pattern and micropapillary tumor pattern in a single-center Asian cohort of 950 patients with resected lung adenocarcinoma. The vast majority of the patients (666 out of 950 patients) harbored lung adenocarcinoma of tumor stage I (3). In this study, the authors propose that a cutoff of 20% CGP discriminates the risk for worsened recurrence free survival (RFS) and overall survival (OS), where a CGP greater than 20% is reported to be associated with a lower RFS (36.4 versus 52.8 months) and OS (47.6 versus 57.4 months) (3). The idea that the amount of CGP may impact long-term patient survival has been proposed previously in both American and European cohorts (2,4). However, the current study is the first to compare RFS and OS in patients using different cutoffs of CGP. The cohort was divided into four groups; 0% CGP, 1–19% CGP, 20–49% CGP and 50–100% CGP. Interestingly, the authors found no significant difference in RFS or OS between group 1 (0% CGP) and group 2 (1–19% CGP), nor between group 3 (20–49% CGP) and group 4 (50–100% CGP), arguing that the critical cutoff for CGP as a prognostic marker would be 20% (3). While the study certainly highlights the potential of CGP as an independent discriminator of survival probability in lung adenocarcinoma, additional studies are warranted to establish the potential and impact of CGP as a prognostic factor. Preferably, future studies should include multi-centered investigations with larger cohorts to enable sub-group division with narrower CGP percentage ranges. In addition, the investigated cohort is strongly shifted towards patients with stage I lung adenocarcinoma. Therefore, it should be taken into consideration that while the full cohort displayed significant differences in RFS and OS for a CGP cutoff of 20%, the authors did not see any significant differences in RFS and OS for patients with stage II–III lung adenocarcinoma (3), challenging the validity of a specific CGP cutoff for patients diagnosed with lung adenocarcinoma, irrespective of tumor stage. Future studies are warranted to validate whether CGP cutoffs should be considered for patients with lung adenocarcinoma of stage II and higher, or exclusively for patients with lung adenocarcinoma of stage I. Nevertheless,

the findings presented by Bai and colleagues lay an important foundation for additional investigations of the prognostic potential of CGP in lung adenocarcinoma.

Moreover, the authors investigated genetic aberrations in seven genes (*KRAS*, *EGFR*, *ALK*, *HER2*, *BRAF*, *ROS1* and *RET*), commonly associated with lung cancer, in the full cohort. The vast majority of patients displayed aberrations in the gene encoding the epidermal growth factor receptor (EGFR) (624 out of 950 patients), followed by aberrations in the genes encoding Kirsten rat sarcoma virus (KRAS) (55 patients), anaplastic lymphoma kinase (ALK) (26 patients), Ret proto-oncogene (RET) (14 patients), B-Raf proto-oncogene (BRAF) (9 patients), human epidermal growth factor receptor 2 (HER2) (9 patients) and Ros proto-oncogene 1 (ROS1) (3 patients). When correlating genetic aberrations with CGP percentage, the authors found that *EGFR* aberrations were significantly correlated with lower CGP percentage (<20%) while *KRAS* and *ALK* aberrations were significantly correlated with higher CGP percentage (>20%). No significant difference was observed for patients with aberrations in *HER2*. Patients with aberrations in *BRAF*, *ROS1* and *RET* were not analyzed for statistical association with CGP percentage (3). It is somewhat difficult to grasp why genetic aberrations in *EGFR*, specifically, should be associated with a lower CGP percentage and, conversely, genetic aberrations in *KRAS* and *ALK* associated with a higher CGP percentage, when the authors did not observe any differences in survival comparing EGFR-positive versus KRAS-positive or ALK-positive patients. In recent years, multiple targeted therapies have reached the clinic for patients with lung adenocarcinoma harboring activating mutations in the kinase domain of EGFR. Due to the successful treatment outcome of employing tyrosine kinase inhibitors, EGFR-positive patients are expected an increased lifespan compared to EGFR-wildtype patients, which was also observed by the authors in this study. Today, EGFR tyrosine kinase inhibitors (TKIs) are offered in the adjuvant setting to patients with resected EGFR-positive lung adenocarcinoma (3,5-10). The variety of adjuvant therapies given to the patients included in this study, likely impacting RFS and OS, makes it nearly impossible to properly assess the survival between the different subgroups based on specific genetic aberrations. Moreover, since the current study was based on a single-centered retrospective cohort, the reported results on the association of aberrations in *EGFR* with lower CGP should be taken with caution. The prevalence of genetic aberrations in *EGFR* is up to four times higher in Asians compared to Caucasians. Moreover, standard-of-care treatment of lung adenocarcinoma patients with aberrations in *EGFR* may vary depending on the geographic location (11). Likewise, it is challenging to comprehend why genetic aberrations in *KRAS* or *ALK* should be associated with an increased CGP percentage, in particular aberrations in *KRAS* which protein product is functionally downstream of EGFR. It is possible that the number of patients in each subgroup could partly explain the conflicting results, i.e., the negative association of genetic aberrations in *EGFR* with CGP percentage (624 patients) versus the positive associations of genetic aberrations in KRAS (55 patients) and ALK (26 patients) with CGP percentage. However, the intriguing findings by Bai and colleagues emphasize the need to look at the association between CGP percentage and specific genetic aberrations in additional and highly controlled clinical cohorts. Hopefully, future studies will specifically look into these findings and possibly validate the associations between *EGFR*, *KRAS* and *ALK* with the percentage of CGP in lung adenocarcinoma patients. As an extension to such studies, it would be interesting to investigate the association of CGP percentage with genetic aberrations in *BRAF*, *RET* and *ROS1*, all representing less prevalent but targetable genetic drivers.

In conclusion, while several aspects should be taken into consideration when evaluating the potential impact of the study from Bai and colleagues, their findings certainly add an important layer of knowledge to the field of lung oncology, potentially aiding in future grading systems of pulmonary adenocarcinoma. Specifically, the results of their study highlight the possibility of using CGP percentage as an independent predictor of survival probability in patients with resected lung adenocarcinoma of stage I.

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Footnote

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