Lung cancer prognosis: can histological patterns and morphological features have a role in the management of lung cancer patients?

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Non-small cell lung cancer (NSCLC) represents approximately 85–90% of all lung cancers. Its incidence is still raising and it remains the leading cause of cancer related death, worldwide, in both sexes (1). Adenocarcinoma (ADC) and squamous cell carcinoma (SCC) represent the major subtypes, even if their incidence is reversing. In fact, ADC accounts for 50% of all lung cancer and its incidence has increased greatly in the last years (2). Currently, many treatment options are available for these patients. However, their prognosis remains poor, suggesting that reliable bookmakers are strongly required in order to guide treatment decisions and optimize patients' outcome. In fact, in the era of precision medicine, identifying the best therapeutic strategy for each patient, based on clinical and biological characteristics of the patient of the disease is crucial. Several prognostic factors have been identified, such as gender, performance status, histology, stage, hyponatremia, systemic inflammation and response to previous treatment, in order to identify subgroups of patients with different prognosis and thus candidates for different therapeutic options (3-5). However, at the moment histology and bimolecular features remain the most important hallmarks to set up the therapeutic approach for advanced lung cancer patients (6). But is histotype enough to choose the correct treatment strategy for each patient? Probably histological subtype growth patterns and tumor microenvironment should be also considered. In fact many studies showed that within the two main histotypes (ADC and SCC), different growth patterns are present and associated to different grading and prognosis (7). In particular ADC includes various invasive patterns belonging to three prognostic groups, such as lepidic pattern, grade 1, acinar and papillary pattern, grade 2, micropapillary and solid pattern, grade 3. The SCC also provides three variants: keratinising, non-keratinizing and basaloid form. While micropapillary and solid pattern are associated to a higher risk of metastasis and poorer prognosis (8), lepidic ADCs are usually associated to a lower internship and to a better prognosis. Acinar and papillary ADC are generally in an intermediate group, with a less predictable impact in patients outcome (9). Otherwise, few and controversial data are available about the predictive role of histological growth pattern in the adjuvant setting (10-12), no data are available in the advanced setting. However, lung cancer is often heterogeneous and different growth patterns can coexist in the same tumor. Therefore, it is important to detect other characteristics such as the presence of elements of differentiation as keratinization in SCC, which is associated with a better prognosis (9). Nevertheless it is not easy for pathologists identifying them by the naked eye.

Furthermore, tumor microenvironment, such as immune cells tumor infiltration and angiogenesis, seems play a crucial role in carcinogenesis, tumor prognosis and response to therapy, especially for immunotherapy (13). At present several immunotherapy agents have proven their efficacy in the treatment of NSCLC patients, but no predictive factors, except the expression of PD-L1 for pembrolizumab, have been identified (14). The study of cell characteristics, the tumor microenvironment and the interaction between them might help to identify patients who will benefit most from immunotherapy. Therefore, future research should be addressed in the study of the aforementioned features. However, one of the main problems is related to the subtype classification system and to the detection of tumor morphological characteristics, which still remains a subjective interpretation of highly-complex pathological images by a pathologist, with considerable rates of inter- and intra-observer variations.

In a recent issue of the *Journal of Thoracic Oncology*, Luo *et al.* published a retrospective computer-aided pathological analysis, that they conducted on 523 ADC and 511 SCC pathological images, downloaded from the Cancer Genome Atlas (TCGA) dataset (15). In particular from the aforementioned pathological images, they extracted 943 morphological features of tissue texture, cells, nuclei and neighboring architecture, identifying 18 morphological features that are significantly associated with prognosis in ADC ($P<0.05$) and 12 in SCC ($P<0.05$). Very interestingly, they developed a statistical prediction model based on these extracted features, stratifying patients into high-risk and low-risk groups, for each histotype. In particular, at multivariate analysis, they observed higher risk of death in the predicted high-risk groups, both among ADC patients (HR =2.34, 95% CI, 1.12–4.91; P=0.024) and SCC patients (HR =2.22, 95% CI, 1.15–4.27; P=0.017), after adjusting for age, gender, smoking status and pathologic tumor stage.

Although this is a pioneering study and results should be confirmed by prospective studies, this study reinforces the idea that according to each specific histotype, tumor morphological characteristics are prognostic factors to take into account in the management of NSCLC patients. Furthermore, this data are confirmed regardless of the stage, suggesting a potential role in therapeutic decision both in early and advanced stages. In particular, in this setting, tumor morphological characteristics, in addiction to clinical and laboratoristic characteristics, should be considered in order to optimize the management of the patients and to identify the better therapeutic approach. However, in order to avoid the limits due to subjective interpretation of pathological images, a computer-aided analysis might be useful.

In conclusion, the detection of histological features is important to assess NSCLC patients' outcome. A computer-aided pathological analysis, when validated, might represent a valid item, both for pathologists and clinicians, for diagnosis and therapeutic strategy of lung cancer patients. In the future, this computational approach could be integrated with the molecular and clinical testing analysis for a better understanding of the pathogenic mechanisms underlying lung cancer and therefore used to improve patient outcomes through tailored therapy.

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Footnote

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

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