



Two phenotypes that predict prognosis in lung adenocarcinoma

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Histopathological biomarkers can predict survival in patients with resected lung adenocarcinoma
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A lung cancer patient's prognosis is defined by a combination of the cancer stage, which defines the cancer location and spread; the patient's performance status, acting as an indirect measure of their ability to tolerate treatment; and finally, more intrinsic tumour-related properties such as the local immune contexture and tumour genetic makeup. The latter two dictate whether immunotherapy and targeted agents are treatment options.

Gauging prognosis is important for both patient and clinician; for the patient, to plan their future, and for the clinician to anticipate what the clinical trajectory is likely to be, enabling timely engagement of relevant healthcare professionals. Understanding a tumour's molecular landscape both informs treatment strategy and predicts likely routes of tumour resistance [1]. Current tools that help predict prognosis are imprecise, especially for lung adenocarcinoma, a condition for which many patients share similar pathology, gene mutations and stage of disease, yet experience hugely diverse outcomes.

Adenocarcinoma is the most common subtype of lung cancer worldwide [2]. Diagnosis requires evidence of either glandular differentiation, mucin production or pneumocyte marker expression [3]. The morphology and extent of neoplastic gland formation can predict patient outcome [4–6]. Cribiform, solid and micropapillary growth patterns have adverse prognostic significance [4, 7]. Local lymphovascular, parietal pleural and chest wall invasion similarly impact survival [7]. Survival after curative resection of early stage lung adenocarcinoma also varies [8]. The metastatic potential of tumour cells is complex and not simply a function of increasing tumour size. The underlying transcriptome/proteome, together with the tumour microenvironment, governs the tumour's ability to transition to a migratory, and therefore metastatic, phenotype [9]. As a community, we need to better predict a tumour's future behaviour to guide treatment decisions and prognosticate. As an example, using another organ, a gene expression assay is available for oestrogen-positive, HER2-negative breast cancer. This assay quantifies the risk of breast cancer recurrence and is used to inform chemotherapy treatment decisions [10]. Importantly, it is able to predict those patients who will benefit from adjuvant chemotherapy following surgery as only 15% of oestrogen-positive, HER2-negative breast cancer patients experience recurrence at 5 years in the absence of adjuvant chemotherapy [11].

Over half of adenocarcinoma cases are driven by a targetable oncogene [12, 13], but as already highlighted, even amongst subgroups of patients who share the same driver oncogene *e.g.* EGFR mutant tumours, molecular and clinical heterogeneity exists [14–16]. The diverse patient outcomes despite sharing the same oncogene can be explained by a number of factors that include the location of the mutation within the gene; the timing of the mutation's occurrence during the tumour's evolution; the presence of more than one driver mutation within the tumour; and the tumour's local immune environment [17]. As a community, we must challenge the single oncogene paradigm in lung adenocarcinoma that encourages us to treat and follow patients up in uniform fashion if they harbour the same oncogene mutation. Biomarkers are needed to better predict treatment response and prognosis. The area this will most likely impact clinically is in assisting adjuvant treatment decisions in “curative” resection cases: a real unmet need given the variability in survival rates [8].

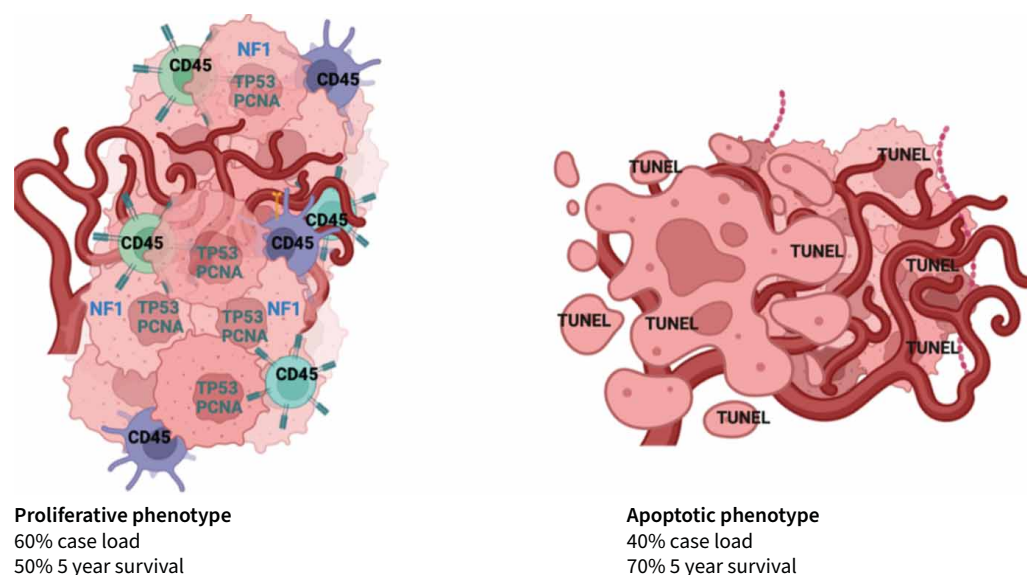


FIGURE 1 Schematic outlining the two proposed phenotypes that inform prognosis in lung adenocarcinoma (drawn using BioRender).

In this issue of the *European Respiratory Journal*, LAMORT *et al.* [18] propose a new set of biomarkers to risk stratify patients with lung adenocarcinoma, in the hope this may better inform prognosis and guide more tumour-centric treatment plans. The team identified two tumour phenotypes based on seven histopathological biomarkers. These biomarkers were able to predict overall survival amongst a cohort of 200 adenocarcinoma cases. The cases selected covered the whole range of TNM7 stages: 64% of cases were either stage I or II, 32% were stage III and 4% were stage IV. The biomarkers distinguish a proliferative phenotype with a worse overall survival compared to an apoptotic phenotype (figure 1). The two clusters did not correlate with growth pattern, driver mutation (40% of cases) or TNM stage, these being the current standard of care from which we derive prognostic information, solidifying the argument that we do need new tools other than those currently available. Patients with “proliferative” tumours (60%) identified by elevated TP53, NF1 (marker of KRAS pathway activation), CD45 and PCNA (marker of cellular proliferation) had a 50% 5-year overall survival, compared to a 5-year survival of 70% amongst the “apoptotic” phenotype, identified by high TUNEL (a marker of tumour cell apoptosis) staining. Breaking away from current prognostic models, clinical and pathological stage predictors such as sex, smoking status, growth pattern and TNM stage do not feature in the model. Intriguingly, their biomarker model demonstrates that the presence of immune cells (CD45+) is associated with worse overall survival; characterising the cell types in these infiltrates further would be informative as previous work has shown increased lymphocytic infiltration to improve survival [19, 20].

The largest benefit of the phenotyping described by LAMORT *et al.* [18] could be in aiding our decision-making process when deciding which patients receive adjuvant treatment, akin to the transcriptional predictor for breast cancer described previously. This would likely lessen the variability we see in survival following curative resection. Clinical trials of non-targeted therapies should consider using this way of tumour phenotyping for treatment allocation. Additionally, following curative resection, patients are followed up for several years with regular imaging to monitor for disease recurrence. This proposed biomarker classification may alter imaging surveillance protocols by prompting the clinician to perform a more frequent follow-up approach for “proliferative” tumours. The authors provide a formula and nomogram to easily generate a score following the tumour’s phenotyping: there are three tiers of score—high, intermediate and low—which correlate with overall survival. The markers are detected using readily available lab assays and scored semi-quantitatively, allowing clinical uptake of this model in countries that are less well resourced. This approach contrasts with the breast cancer prognostic model requiring the tumour’s transcriptome to be sequenced [21, 22], which is expensive and time consuming.

As the arsenal of agents available to treat lung cancer is expanding dramatically, we need a choice of biomarkers to decide if (and probably when) to use therapeutic agents. The tumour microenvironment and genetic configuration of tumours currently play a more important role in delineating treatment choice than

the pathology of non-small cell lung cancer, which only subtly affects treatment strategy. However, the prognosis for single oncogene-driven lung adenocarcinomas is more complicated than a “one size fits all” approach. An appropriate use for the novel biomarkers and scoring systems proposed by Lamort *et al.* [18] might be to influence post-surgical clinical decisions in less advanced tumours.

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