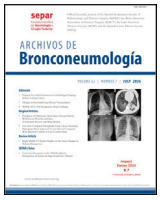
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

separ
Sociedad Española de Neumología y Cirugía Torácica

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial

Tumor Heterogeneity and Metastatic Potential in Lung Cancer: How Early Can a Tumor Become Metastatic?

Lung cancer remains one of the leading causes of cancer related deaths worldwide, with metastatic disease accounting for the majority of deaths from solid tumors [1]. In early-stage non-small cell lung cancer (NSCLC), a large proportion of patients still recur despite successful surgery with curative intent [2]. This raises key considerations: when do tumors first metastasize, and how rapidly should we act to detect and then resect or treat the tumor? Additionally, could earlier detection of disseminated disease, before macroscopic recurrence, create a window for more effective adjuvant treatment?

One of the reasons metastatic potential is still poorly understood is because tumors are heterogeneous—many cell populations, or 'subclones', arise from a single common ancestral cell and evolve in parallel to one another, leading to branched evolution through principles of natural selection. Understanding this heterogeneity and the interplay between different cell populations and its effect on patient outcome is critical to better understanding the metastatic process.

The TRACERx study is a UK-wide prospective clinical trial which recruited patients with early-stage, untreated NSCLC and followed them for up to 5 years through their disease course; it aims to better understand these questions by investigating the relationship between intratumor heterogeneity (ITH) and disease recurrence. By performing multi-region tumor sampling at diagnosis and longitudinal follow-up, the TRACERx study characterizes tumor evolution through space and time.

One of the main questions the TRACERx study has attempted to address is understanding differences between primary tumors that metastasize and those that do not and following this up further by characterizing cell populations within the primary tumor that subsequently give rise to metastases (so-called metastatic seeding clones). To this end, we have shown that high tumor heterogeneity at the somatic copy number level is associated with rapid extrathoracic relapse while low copy number heterogeneity is associated with intrathoracic relapse occurring after more than 1 year [3]. Additionally, patients with tumors where at least one subclone has undergone a recent local expansion, i.e. rapid growth at the "tips" of a tumor's evolutionary tree, and shows evidence of subclonal selection have shorter disease-free survival compared to patients with tumors without recent subclonal expansions [3]. Furthermore, clones that go on to seed metastases are larger and more dispersed in the primary tumor and genes associated with lung cancer show signs of positive selection [2]. Additionally, these metastatic seeding clones were significantly more expanded in preoperative plasma than non-metastatic subclones [4]. Combined, this highlights that the metastatic clone is already dominant within the primary tumor at the time of surgery.

By using paired primary and metastasis data, it is possible to characterize the metastatic seeding clones within the primary tumor and, through detailed annotation, track where these clones disseminate within the body. In a subset of cases, multiple clones within the primary tumor have metastatic potential and either go on to seed one metastasis together or each clone seeds separate metastases. We refer to this as 'polyclonal dissemination' and found that this was associated with extrathoracic disease recurrence [2]. When considering initial metastatic spread, primary lymph node disease contributed to metastatic relapse in less than 20% of cases, therefore likely representing a hallmark of metastatic potential rather than a route to subsequent disease progression [2]. Although both the primary tumor and lymph node metastases were resected at the same time, the assumption is that the latter arose more recently and therefore might not have had sufficient time to give rise to additional metastases, highlighting the benefit of extensive surgical intervention. In fact, a recent study shows a link between the duration metastases were in situ and the likelihood of them seeding further metastases [5]. More than half of sampled metastases were seeded by other metastases rather than directly by the primary tumor and most metastasis-to-metastasis migrations occurred within the same anatomical cavity (i.e. intra- or extrathoracic), while primary-to-metastasis migrations were equally likely to lead to intra- and extrathoracic metastases [5].

Given that metastases can occur in various organs and therefore in different microenvironments compared to the primary tumor, it is unclear whether they are subject to the same evolutionary pressures. Therefore, it is important to understand whether it is possible to use the primary tumor to inform our understanding of metastases. Various models of metastatic progression have been described. In a linear progression model, metastatic potential accumulates over time, and the metastatic clone arises late in tumor evolution, meaning the majority of genomic events are shared between the primary tumor and its metastases. By contrast, in a parallel progression model, the metastatic clone diverges and disseminates early, with both the primary tumor and metastases continuing to evolve independently, leading to high genomic diversity between them [6]. Understanding the timing and spread of metastases has important clinical implications. If metastases occur late in tumor evolution, it is likely that a large proportion of primary tumor mutations are shared with the metastases making targeted

https://doi.org/10.1016/j.arbres.2026.08.019
0300-2896/© 2026 SEPAR. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Please cite this article as: A. Huebner, Tumor Heterogeneity and Metastatic Potential in Lung Cancer: How Early Can a Tumor Become Metastatic? Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2026.08.019

therapies informed by the primary tumor effective. Additionally, by detecting the primary tumor earlier metastatic divergence and dissemination could be prevented.

Analysis of the TRACERx paired primary-metastatic cohort showed that metastases generally diverge late, after the last clonal sweep in the primary tumor. This highlights that in most cases, early detection will likely reduce disease recurrence and improve patient outcome. Early divergence was enriched for patients who were smokers at the time of diagnosis, a finding with potential relevance to screening programs targeting these high-risk individuals. Simulations suggested that early divergence more frequently occurred at smaller tumor diameters (less than 8 mm), and usually below the level of clinical actionability [2,7]. Crucially, single-region primary tumor sampling misclassifies 83% of late-divergence cases as early divergence. This implies that studies based on single biopsies might be overestimating the prevalence of early metastatic divergence and therefore underestimating the benefit of early detection to improve patient outcomes, given that intervention might still precede metastatic dissemination. This finding highlights the importance of multi-region sampling or longitudinal sampling through liquid biopsies to accurately resolve metastatic timing and, in turn, better define the window in which earlier interventions such as surgery could prevent metastasis.

Circulating tumor DNA (ctDNA) has emerged as the most powerful non-invasive tool for tracking metastatic subclonal dynamics. A companion TRACERx study analyzing 2994 plasma samples from 431 patients, showed that patients with lung adenocarcinoma (LUAD) where no ctDNA was detected prior to surgery had significantly better outcome compared to ctDNA-positive LUAD patients [8]. Post-surgical ctDNA surveillance detected residual molecular disease in 29% of patients within 120 days of resection and may help stratify patients further [8]. These data position ctDNA not only as a prognostic biomarker but as a potential trigger for adjuvant intervention—an approach being evaluated further in clinical trials such as MERMAID and APPLE [9,10].

The old paradigm of metastasis as an event at the end of the tumor's natural history is no longer tenable for a significant subset of lung cancers and should reshape how we conceptualize 'early-stage' lung cancer. A tumor smaller than a centimeter may already have disseminated and seeded future metastases in a polyclonal, organ-selective fashion. Resection alone, however complete, cannot address disseminated micro-metastatic disease, which is why a proportion of stage I patients relapse despite clear surgical margins. The imperative now is to translate this biological knowledge into clinical action: identifying the metastatic clone and intervening before it disseminates or before its recurrence is evident macroscopically.

Artificial intelligence involvement

None of the material has been partially or totally produced with the help of any artificial intelligence software or tool.

Funding of the research

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

References

[1] Dillekås H, Rogers MS, Straume O. Are 90% of deaths from cancer caused by metastases? Cancer Med 2019;8:5574–6.
[2] Al Bakir M, Huebner A, Martínez-Ruiz C, Grigoriadis K, Watkins TBK, Pich O, et al. The evolution of non-small cell lung cancer metastases in TRACERx. Nature 2023;616:534–42.
[3] Frankell AM, Dietzen M, Al Bakir M, Lim EL, Karasaki T, Ward S, et al. The evolution of lung cancer and impact of subclonal selection in TRACERx. Nature 2023;616:525–33.
[4] Abbosh C, Frankell AM, Harrison T, Kisistok J, Garnett A, Johnson L, et al. Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. Nature 2023;616:553–62.
[5] Hessey S, Bunkum A, Huebner A, Haase K, Grigoriadis K, Naceur-Lombardelli C, et al. Evolutionary characterization of lung cancer metastasis. Nature 2026;653:911–22.
[6] Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer 2009;9:302–12.
[7] MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology 2017;284:228–43.
[8] Black JRM, Karasaki T, Abbott CW, Li B, Veeriah S, Al Bakir M, et al. Longitudinal ultrasensitive ctDNA monitoring for high-resolution lung cancer risk prediction. Cell 2025;188:7083–98, e18.
[9] Spigel DR, Peters S, Ahn M-J, Tsuboi M, Chaft J, Harpole D, et al. 93TiP MERMAID-2: phase III study of durvalumab in patients with resected, stage II-III NSCLC who become MRD+ after curative-intent therapy. J Thorac Oncol 2021;16:S745–6.
[10] Remon J, Besse B, Aix SP, Callejo A, Al-Rabi K, Bernabe R, et al. Osimertinib treatment based on plasma T790M monitoring in patients with EGFR-mutant non-small-cell lung cancer (NSCLC): EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial. Ann Oncol 2023;34:468–76.

Ariana Huebner [a,b]
[a] *Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London, UK*
[b] *Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK*
E-mail address: ariana.huebner.16@ucl.ac.uk