npj primary care respiratory medicine

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The "Asian Paradox" in multiple primary lung cancer: a geographic monopole driven by phenotypic divergence

The global clinical trial landscape for multiple primary lung cancer (MPLC) exhibits a striking geographic anomaly. Through a systematic analysis of 8212 lung cancer registrations (2015–2024), we identified a cohort of 17 trials explicitly targeting MPLC. Analysis revealed an absolute geographic monopole: 100% of these trials were investigator-initiated in China, with a complete absence of active protocols in Western registries. We argue that this segregation is not accidental but driven by the "Asian phenotype",which is characterized by indolent, multifocal ground-glass nodules (GGNs), demands lung-sparing local strategies distinct from the systemic paradigms favored in the West. We urge the international community to transition from universal guidelines to phenotype-stratified management frameworks.

npj Primary Care Respiratory Medicine (2026)36:23 ;
https://doi.org/10.1038/s41533-026-00504-7

THE GLOBAL DIVERGENCE IN MPLC MANAGEMENT

While high-resolution imaging has unveiled a rising tide of multiple primary lung cancer (MPLC), the global response to this clinical entity remains fragmented[1]. In Western oncology, multifocal lung lesions are frequently interpreted under metastatic-leaning clinical and trial-assessment assumptions, often prioritizing systemic control[2,3]. Conversely, in East Asia, the prevalence of synchronous, indolent ground-glass nodules (GGNs) has fostered a distinct clinical perception of MPLC as a locoregional disease requiring preservation of lung parenchyma[4]. This divergence has created a "clinical blind spot": while the patient population is expanding, the generation of high-level evidence remains geographically siloed, leading to a disconnect between global guidelines and regional realities[5].

MAPPING THE EVIDENCE GAP

To quantify this disparity, we conducted a comprehensive registry-based audit of interventional lung cancer trials registered between 2015 and 2024. We queried four major databases (ClinicalTrials.gov[6], ChiCTR[7], EU-CTR[8], and ISRCTN[9]) covering the majority of industry-sponsored and investigator-initiated research across North America, Europe, and Asia. Using a precise Boolean search strategy targeting "multiple primary" and "multifocal" terms, we screened 8212 records to isolate trials specifically designed for the MPLC population, acknowledging that registry text may not consistently label MPLC and could therefore underestimate inclusion when multifocal patients are enrolled without explicit identifiers.

A LANDSCAPE DEFINED BY GEOGRAPHIC AND PHENOTYPIC SEGREGATION

The registry data reveal a striking geographic concentration. Of the 17 identified interventional trials, all (100%) were initiated in China within the queried registries and time window (Fig. 1). In sharp contrast, major Western registries showed no interventional protocols that explicitly targeted MPLC ($n = 0$) in non-China entries within ClinicalTrials.gov, EU-CTR, or ISRCTN. This absolute disparity indicates that the contemporary evidence base for MPLC is being constructed exclusively within the East Asian clinical context.

To decode the drivers behind this "China concentration," we mapped the trajectory from target population to therapeutic intervention (Fig. 2). The data identify a distinct phenotype-driven strategy: 41% ($n = 7$) of the Chinese trials explicitly targeted GGNs, and these trials predominantly employed Local therapies (e.g., ablation, stereotactic body radiation therapy, or sublobar resection) rather than systemic drugs. This pattern supports the interpretation that the GGN-predominant, lung-sparing trial paradigm is a direct adaptation to the regional case-mix enriched for indolent, multifocal GGN-predominant presentations, a disease entity characterized by indolent growth and multifocality, fundamentally differing from the aggressive, solid-tumor models that dominate Western drug development pipelines.

THE "ASIAN PARADOX" AND THE NEED FOR STRATIFIED GUIDELINES

This distinct geographic pattern points to a unique "Asian Paradox": MPLC is biologically ubiquitous but clinically investigated primarily in Asia. We propose that this is not merely an oversight but a reflection of a fundamental regional heterogeneity in dominant clinical phenotypes and trial-ready populations between East and West. The Western research paradigm is calibrated for the "smoker phenotype"—aggressive, solid tumors requiring systemic eradication. In contrast, the surge of investigator-initiated trials in China is a rational response to the "Asian phenotype" of multifocal GGNs, where the primary endpoint is organ preservation rather than just progression-free survival.

Therefore, applying "one-size-fits-all" guidelines to MPLC is scientifically flawed. The international community (IASLC, ESMO, ASCO) must acknowledge this dichotomy. Future frameworks should move beyond generic staging to phenotype-stratified guidelines, endorsing lesion-level interventions for the indolent GGN-predominant, multifocal presentations while reserving systemic protocols for high-risk cohorts. Only by respecting this biological distinctiveness can we bridge the gap between global standards and regional clinical needs.

Fig. 1 The Geographic Monopole of MPLC Research (2015–2024). Map showing the absolute segregation of the 17 identified interventional trials. 100% were initiated by Chinese investigators (red circle), contrasting with a complete absence ($n = 0$) of active protocols in major Western registries (North America/Europe). This highlights an evidence base constructed exclusively within the East Asian clinical context.

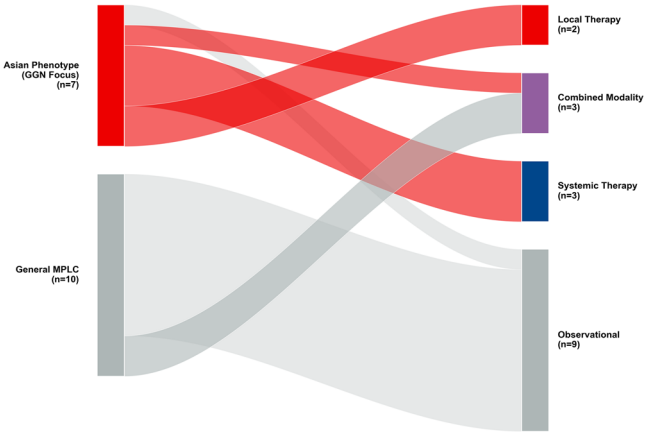

Fig. 2 The "Asian phenotype" Drives Therapeutic Strategy. Sankey diagram mapping target phenotypes (left) to interventions (right) in Chinese trials. The dominant red stream reveals that trials explicitly targeting Ground-Glass Nodules (GGNs) ($n = 7$) preferentially adopt Local Therapies or Combined Modalities. This pattern confirms an adaptation to the indolent, multifocal "Asian phenotype," diverging from the systemic-focused Western paradigms.

DATA AVAILABILITY

No new datasets were generated. The study is based on publicly available trial registry data.

Received: 5 June 2025; Accepted: 14 March 2026;
Published online: 06 April 2026

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ACKNOWLEDGEMENTS

The study was supported by the National High Level Hospital Clinical Research Funding (80102022501).

AUTHOR CONTRIBUTIONS

J.S. led the study design, data analysis, and manuscript writing. Y.G. supervised the study and revised the manuscript. Both authors read and approved the final manuscript.

COMPETING INTEREST

The authors declare no competing interests.

ADDITIONAL INFORMATION

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