# Spatiotemporal heterogeneity in non-small cell lung cancer: A paradigm shift from characterization to dynamic management (Review)

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**Abstract.** Treatment of non-small cell lung cancer (NSCLC) has entered the era of precision medicine, characterized by targeted therapies and immunotherapies. However, tumor heterogeneity across spatial and temporal dimensions remains a central cause of therapeutic failure and acquired resistance. Spatial heterogeneity manifests as clonal diversity within a single tumor and between metastatic lesions, while temporal heterogeneity reflects the dynamic evolution of clonal populations under therapeutic pressure. It has proved difficult for traditional static diagnostic and therapeutic models to comprehensively capture this complexity. Advances in technologies such as single-cell sequencing, spatial transcriptomics and liquid biopsy now allow the spatiotemporal evolutionary patterns of NSCLC to be deciphered with unprecedented resolution. Based on these developments, the present review proposed that clinical management strategies need to shift from a static classification paradigm towards a new paradigm of dynamic monitoring and intervention. Emerging strategies are systematically discussed, including evolutionary trap therapy, niche intervention and adaptive therapy, which aim to achieve long-term control of disease progression by steering tumor evolutionary paths, remodeling the tumor microenvironment or leveraging competitive suppression mechanisms. Despite ongoing challenges at the technical, biological and clinical translation levels, a dynamic management framework integrating multi-omics data and intelligent algorithms represents promise for transforming NSCLC into a chronic, controllable disease.

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**Contents**



## 1. Introduction

Lung cancer remains the most common malignancy and the leading cause of cancer-related death globally, with non-small cell lung cancer (NSCLC) accounting for ~85% of all lung cancer cases and representing the predominant pathological subtype of this disease (1,2). The management of NSCLC has advanced into an era of precision medicine, marked by the development of therapies targeting oncogenic driver genes and immune checkpoint inhibitors (3,4). However, the emergence of acquired resistance remains a primary cause of treatment failure (5). This challenge is rooted in one of the core biological features of NSCLC, namely tumor heterogeneity. It manifests not only within individual tumors (intratumor heterogeneity) but also between different metastatic lesions (intertumor heterogeneity) and markedly evolves over time under the selective pressure of treatment (clonal evolution) (6,7). Traditional, static diagnostic and therapeutic models, e.g., treatment decisions based solely on initial TNM staging, fixed chemotherapy regimens for all patients and non-adaptive radiotherapy planning, typically reliant on single biopsy specimens, are inadequate for capturing this complex dynamic landscape, thereby limiting the durability of treatment efficacy. Recent progress in high-throughput sequencing technologies, particularly the application of single-cell sequencing, spatial transcriptomics and liquid biopsy, has enabled the dissection of the clonal architecture and evolutionary trajectory of NSCLC with unprecedented resolution (8-10). The data generated by these technologies necessitate the establishment of a new conceptual framework capable of integrating spatiotemporal

dynamic information. The present review therefore aimed to propose and elaborate on such a framework, arguing that the clinical management strategy for NSCLC must transition from a static, genotype-based 'one-time strike' approach towards a 'dynamic management' strategy founded on continuous monitoring, with the goal of achieving more prolonged disease control.

## 2. Charting the spatiotemporal atlas of NSCLC: Technological frontiers and biological insights

*Deciphering spatial heterogeneity*. Spatial heterogeneity constitutes the geographical dimension of tumor complexity. Seminal multi-region sequencing studies determined marked intratumor heterogeneity at the genomic level within individual NSCLC tumors (6,7,11). For instance, sequencing different regions of a primary lung lesion may reveal an uneven distribution of mutant alleles with evolutionary importance in driver genes (such as EGFR) and even identify distinct subclonal dominance regions (12). This heterogeneity also extends to gene expression. Single-cell RNA sequencing has revealed continuous and diverse cancer cell states within a tumor, including proliferation, differentiation, epithelial-mesenchymal transition (EMT) and drug response (13). Notably, spatial transcriptomics and multiplex immunofluorescence technologies anchor cellular molecular features to their native tissue microenvironment (8). Studies have found that cancer cell subpopulations with stem-like properties or those in an EMT state are often specifically enriched at the invasive front of the tumor margin, forming complex spatial interaction networks with specific immune cells [such as M2-type macrophages and regulatory T cells (Tregs)] and fibroblasts; these niches influence tumor progression and therapeutic response by promoting immunosuppression, remodeling the extracellular matrix, and secreting pro-survival and pro-invasive factors (14-16).

With regard to intertumor heterogeneity, systematic genomic comparative analyses of different metastatic lesions (including the brain, bone and adrenal glands) have revealed a complex clonal dissemination pattern (Fig. 1). Research has indicated that different metastases may originate from distinct subclonal populations within the primary tumor, forming independently through 'parallel evolution', or arising from a single disseminated subclone that subsequently undergoes independent genomic and phenotypic evolution under the selective pressures of different organ-specific microenvironments (17,18). Recent Tracking Cancer Evolution through therapy/Rx (TRACERx) analyses of 421 patients with NSCLC have determined the evolutionary patterns of metastases. Frankell *et al* (19) found that subclonal whole-genome doubling (19% of tumors) was associated with shorter disease-free survival and Al Bakir *et al* (20) showed that 25% of metastases diverged before the last clonal sweep in the primary tumor; single-region sampling would misclassify 83% of late divergence cases as early dissemination. These findings underscore the need for extensive spatiotemporal sampling to capture clonal architecture. Such differentiation in evolutionary paths results in marked disparities between metastatic sites in the distribution of key driver gene mutations (including EGFR, anaplastic lymphoma kinase and KRAS), tumor mutational burden and immune microenvironment features, such as programmed death-ligand 1 (PD-L1) expression levels and the composition and density of tumor-infiltrating lymphocytes (21-23). This biological process may explain a key clinical challenge: When therapy is targeted against a specific metastasis, failure to effectively cover the dominant, genotypically and phenotypically diverse subclonal populations in other lesions may lead to the rapid progression of these untreated sites in the absence of competitive suppression (24,25). This finding underscores the necessity of fully accounting for intertumor heterogeneity when formulating treatment strategies for advanced NSCLC. It also highlights the importance of combining systemic therapy with local interventions.

*Tracking temporal heterogeneity*. Temporal heterogeneity, referring to the dynamic evolutionary process of clonal populations under therapeutic selection pressure, serves as a primary driver of acquired resistance (6,26). Circulating tumor DNA (ctDNA) sequencing, a mainstay in liquid biopsy, provides a pivotal, non-invasive technical means for the real-time dissection of this evolutionary process (9), enabling the capacity to observe the longitudinal evolution of the genomic landscape in NSCLC.

The core principles of liquid biopsy lie in its utility as a dynamic monitoring tool for clonal evolution. In comparison with the static information provided by single-timepoint tissue biopsies, longitudinal ctDNA analysis enables continuous tracking of the evolutionary trajectory of tumor genomes (9). Quantitative analysis of the variant allele frequency of specific gene mutations allows for inferences regarding dynamic changes in clonal population structure, thereby facilitating the reconstruction of tumor phylogenetic trees (6,7). Notable research has indicated that clonal evolutionary patterns hold marked prognostic importance: Patients exhibiting highly 'branched evolutionary' patterns (such as concurrent development of numerous subclones) typically experience worse clinical outcomes compared with patients exhibiting 'linear evolutionary' patterns, attributable to their higher intratumor heterogeneity and more complex potential resistance mechanisms (6). The TRACERx study quantified branching evolution in NSCLC, whereby Frankell *et al* (19) identified subclonal selection for 22 of 40 common cancer genes in lung adenocarcinoma and copy-number heterogeneity predicted extrathoracic relapse within 1 year after surgery. These NSCLC-specific data reinforce the prognostic importance of branched evolution. Longitudinal ctDNA analyses have also revealed the rise and fall of dominant clones under the pressure of targeted therapy, providing direct evidence for the dynamic selection process of resistant clones (6,9).

Furthermore, ctDNA analysis may serve as an early warning system for resistance-associated genetic alterations. Clinical evidence has demonstrated that the emergence or marked increase in the abundance of resistance-associated gene mutations can be detected in ctDNA prior to the determination of disease progression by radiographic assessment (26-28). Wang *et al* (29) proposed a risk-adaptive stratification strategy integrating baseline ctDNA genotyping with ctDNA-molecular residual disease monitoring to guide individualized decisions regarding consolidation immunotherapy after chemoradiotherapy in locally advanced NSCLC. This study suggested that

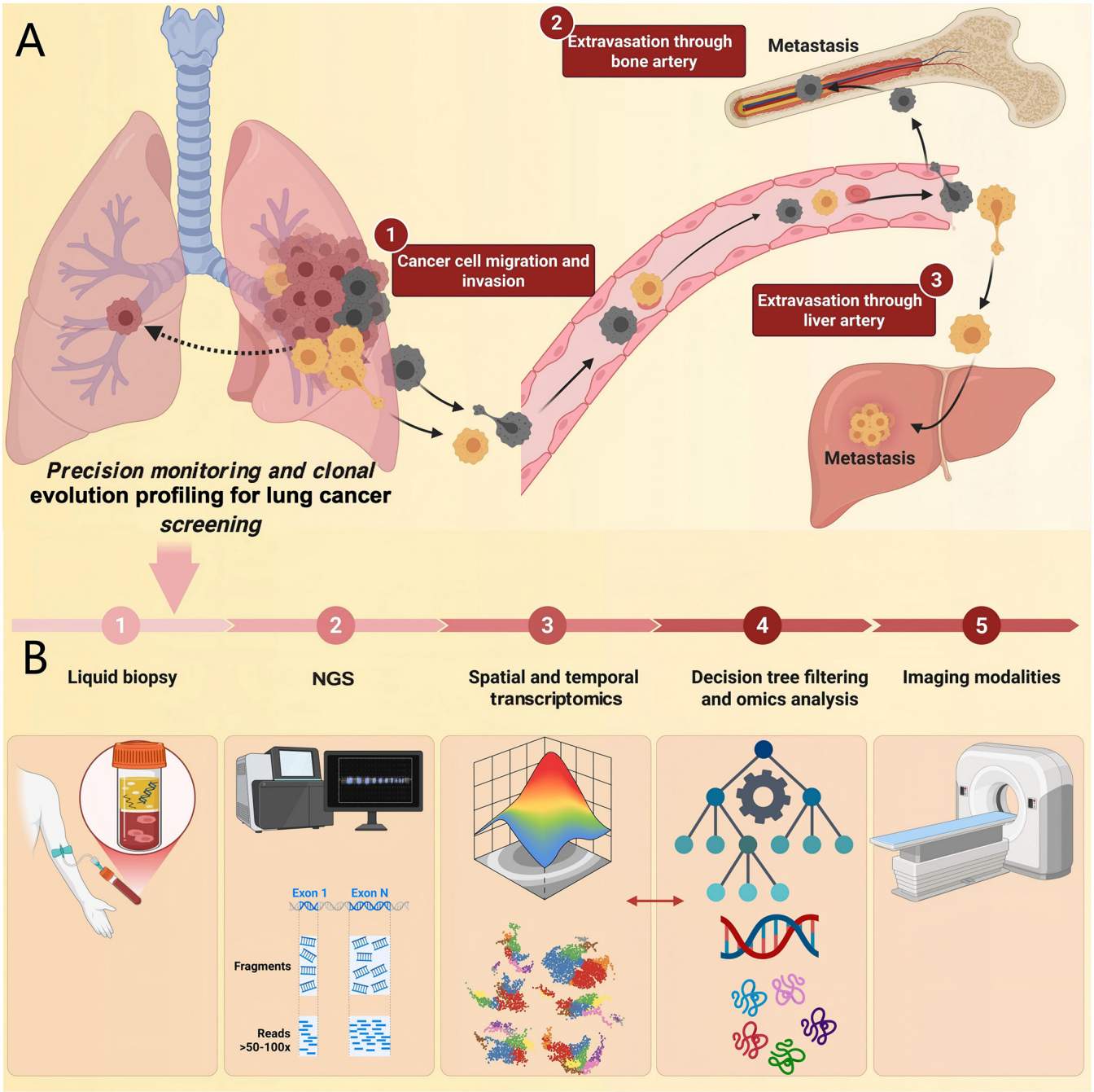


Figure 1. Deciphering the spatiotemporal heterogeneity of non-small cell lung cancer through integrated multi-omics technologies. (A) Spatial multi-omics reveal spatial heterogeneity. Technologies such as spatial transcriptomics and multiplex immunofluorescence delineate intratumor heterogeneity within the primary tumor (cell clusters of different colors represent distinct subclones with unique molecular profiles), as well as intertumor heterogeneity between different metastatic lesions. (B) Serial liquid biopsy tracks temporal heterogeneity. Longitudinal blood sample collection for ctDNA analysis enables non-invasive monitoring of tumor clonal evolution, which facilitates the early detection of resistance mechanisms. ctDNA, circulating tumor DNA; NGS, next-generation sequencing.

serine/threonine kinase 11/kelch-like ECH-associated protein 1 mutations not only predict radiotherapy resistance but also suggest a potential benefit from post-radiotherapy immunotherapy, illustrating an adaptive treatment paradigm guided by genotype-therapy interactions. In EGFR-mutant NSCLC, serial ctDNA monitoring can preemptively identify resistance events mediated by EGFR T790M, C797S mutations (including cis/trans configurations), MET amplification or bypass activation pathways (26). This 'lead time' provides a key window for clinical intervention, making it possible to adjust treatment strategies before the onset of clinical symptoms or radiographic progression, thereby fostering novel clinical management paradigms such as 'pre-emptive therapy' (30). Notably, ctDNA abundance shows a notable positive association with total tumor burden in the body, establishing it as a highly sensitive pharmacodynamic biomarker (31,32). A rapid decrease or clearance of ctDNA levels following therapeutic intervention has been markedly associated with objective response rate and longer progression-free survival, whereas the persistence or early rebound of ctDNA levels often indicates poor treatment

response or primary resistance (28,32). This dynamic profile provides a rationale for the real-time assessment of therapeutic efficacy and for the future exploration of biomarker-guided adaptive therapy strategies. Beyond ctDNA, other components of liquid biopsies, such as circulating tumor cells (CTCs) and tumor-derived exosomes, can provide complementary information (33,34). CTCs can be utilized for *in vitro* functional studies, while exosomes carry molecular information including proteins and RNA, aiding in the analysis of tumor phenotypic states and intercellular communication (35,36).

Despite this, given the relative advantages of ctDNA analysis with regard to technical standardization, detection sensitivity and specificity and clinical accessibility, it currently remains the most widely used and evidence-supported component of liquid biopsy in both research and clinical practice (37,38). Fig. 1 illustrates how primary tumor subclones disseminate through the bloodstream to the bone and liver, forming metastatic lesions with distinct characteristics (spatial heterogeneity). Serial liquid biopsy tracks ctDNA dynamics, in which changes in allele frequency reveal clonal evolution and the emergence of early resistance. This real-time monitoring enables pre-emptive intervention before radiographic progression, thereby translating heterogeneity into an actionable clinical strategy.

## 3. Emerging therapeutic paradigms addressing spatiotemporal heterogeneity

In response to the challenges posed by heterogeneity, novel therapeutic strategies are shifting from a sole focus on 'maximal cell kill' towards more strategic management.

*Evolutionary trap therapy: Steering tumor evolution.* This concept, drawing from evolutionary biology, aims to actively steer tumor clonal populations towards evolving into states that are more drug-sensitive or confer a proliferative disadvantage rather than passively awaiting the emergence of resistance. Its theoretical basis leverages the fitness cost experienced by resistant cancer cells relative to their sensitive counterparts in specific contexts (25,39). For instance, clones resistant to certain EGFR inhibitors may regain sensitivity to chemotherapeutic agents or become dependent on a targetable bypass signaling pathway (40,41). Clinical applications include alternating therapies with distinct mechanisms of action or employing low-dose metronomic chemotherapy. These strategies aim to suppress dominant clones while preserving populations of sensitive cells that can suppress the expansion of resistant clones, thereby preventing their rapid proliferation due to 'competitive release' (39,42).

*Niche intervention: Remodeling the microenvironment 'soil'.* Niche intervention strategies have represented a shift in therapeutic paradigm. The core premise lies in targeting the tumor microenvironment (TME), which sustains cancer cell survival, promotes proliferation and mediates immune escape. This may prove more effective compared with direct targeting of the heterogeneous cancer cells themselves. This strategy is based on the understanding that the TME, acting as the 'soil' supporting tumor growth, promotes disease progression by facilitating immune evasion, angiogenesis, invasion and metastasis (43,44). Consequently, systematically remodeling this microenvironment from a pro-tumor to an anti-tumor state can indirectly and sustainably control the proliferation, invasion and development of acquired resistance in diverse cancer cell 'seeds' within it. Compared with directly targeting genotypically diverse and dynamically evolving tumor cells, niche intervention acts upon relatively stable host-derived components of the TME, thereby offering broader therapeutic applicability and the potential for more durable efficacy.

A primary direction of niche intervention is reversing the immunosuppressive microenvironment, which is densely infiltrated by M2-type tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and Tregs. These cells create a physical and functional barrier that impairs effector immune cells through inhibitory cytokines, immune checkpoint molecules and metabolic competition (45,46). Targeting key recruitment and activation pathways of these cells, for instance, depleting M2 macrophages by antagonizing colony-stimulating factor 1 receptor or inhibiting MDSC recruitment by blocking C-C chemokine receptor (CCR)-2/CCR5 signaling, has been shown in preclinical models to convert immunologically 'cold' tumors (T-cell-poor, non-inflamed) into 'hot' ones (T-cell-rich, inflamed), thereby restoring the capacity of the host immune system to recognize and eliminate diverse cancer cell clones (47-49). TAMs serve a central role in NSCLC progression. Larionova *et al* (50) demonstrated that TAMs secrete VEGF amongst other pro-angiogenic factors, including semaphorin, S100A family members and chitinase-like proteins, limiting the efficacy of anti-angiogenic therapy. In addition, Huang *et al* (51) systematically summarized TAM-mediated resistance mechanisms in NSCLC and proposed targeting TAMs to overcome resistance. Meanwhile, cancer-associated fibroblasts (CAFs) participate in immune regulation by suppressing immune cell function and promoting immune evasion, primarily through upregulation of COX2/PD-L1 and secretion of TGF-β/IL-10 (52). These findings suggest that targeting TAMs and CAFs to remodel the tumor microenvironment niche represents a promising therapeutic strategy for NSCLC. In addition, targeting the TGF-β signaling pathway may not only suppress the activation of cancer-associated fibroblasts, but also alleviate its potent suppression of T cell function, demonstrating dual potential in reshaping the immune microenvironment (53,54).

An additional key strategy involves targeting the metabolic niche of the tumor. Tumor cells, through reprogramming their own metabolism and engaging in metabolic coupling with stromal cells within the TME, promote a local environment that is acidic, hypoxic and nutrient-depleted. This environment, in turn, selects for and promotes the expansion of more adaptable clones (55-57). Drugs targeting key metabolic pathways shared by tumor cells and immune cells, such as adenosine pathway antagonists (e.g., A2A/A2B receptor antagonists like inupadenant and PBF-1129, and CD73 inhibitors like oleclumab and uliledlimab) and IDO1 inhibitors (e.g., epacadostat), aim to ameliorate nutrient competition within the TME and relieve metabolic immunosuppression, thereby indirectly inhibiting cancer cell growth (58,59).

Furthermore, intervening in the formation of the pre-metastatic niche represents a long-term application of niche intervention. The primary tumor systemically remodels

the microenvironment of distant organs via secreted factors (e.g., TGF-β, VEGF, LOXL2) and tumor-derived exosomes (carrying integrins, miRNAs and proteins), making them more conducive for the colonization of circulating tumor cells, thus forming a pre-metastatic niche (60-62). Research has suggested that targeting key molecules involved in this process, such as TGF-β and lysyl oxidase-like 2, may disrupt the 'seeding' process of metastasis in specific organs, spatially restricting the success rate of clonal dissemination (63-65).

Radiation therapy is also emerging as a potential tool for niche intervention. Traditionally viewed primarily as a local cytotoxic modality (66), recent studies have indicated that radiotherapy can systemically reshape the TME by inducing immunogenic cell death, releasing tumor-associated antigens and inflammatory factors, thereby activating anti-tumor immune responses and exerting an '*in situ* vaccine' effect (67-69). Among radiotherapy techniques, stereotactic body radiotherapy (SBRT), known for its high precision and high biologically effective dose, has garnered notable attention for its ability to modulate the tumor immune microenvironment (70). Studies have demonstrated synergistic effects when SBRT is combined with immune checkpoint inhibitors (70-72). For example, a randomized phase II trial showed that SBRT combined with nivolumab markedly increased the response rate of non-irradiated distant lesions (the 'abscopal effect') demonstrating that SBRT can induce a systemic anti-tumor immune response (72). This finding highlights the paradigm shift of radiotherapy as a niche intervention tool, moving from local modulation to systemic immune activation.

Metabolic niche intervention represents another emerging frontier. Research has indicated that the composition of the gut microbiota is a key regulator in the efficacy of programmed cell death protein 1/PD-L1 inhibitors, with the abundance of specific beneficial bacterial species being associated with improved treatment response, thus offering a new target for improving immunotherapy through microbiota modulation (73). Shan *et al* (74) reported a novel laser desorption/ionization time-of-flight mass spectrometry method based on a gold nanoparticles/cellulose nanocrystals nanocomposite for direct and highly sensitive detection of intact proteins in NSCLC serum exosomes. This method identified five characteristic proteins, namely S100 calcium binding protein A10, urokinase-type plasminogen activator receptor, C1 inhibitor, FGR proto-oncogene, Src family tyrosine kinase and mannan-binding lectin serine protease-2, as effective predictive biomarkers of NSCLC risk, offering a new technical avenue for liquid biopsy. On the other hand, in-depth studies of driver mutations such as isocitrate dehydrogenase $1^{R132H}$ reveal that they induce profound metabolic reprogramming in tumor cells by prompting the production of unique oncometabolites (including 2-hydroxyglutarate) (75-77). This distinct metabolic dependency itself presents a promising window for therapeutic intervention.

In summary, the niche intervention strategy, by systemically modulating the local and systemic environments upon which tumors depend, offers a novel approach to overcoming the challenges posed by tumor heterogeneity to direct targeting strategies. Despite this field facing challenges such as target specificity, off-target effects and a lack of biomarkers, its therapeutic philosophy, aimed at altering the fundamental properties of the tumor ecosystem, represents a key evolutionary direction in cancer treatment paradigms.

*Adaptive therapy: Model-based dynamic control*. Adaptive therapy represents a paradigm shift, transitioning the therapeutic objective from 'maximal cell kill' towards the long-term control of tumor population dynamics. Grounded in evolutionary dynamics, this strategy aims to stabilize tumor burden at a controllable level by modulating therapeutic selection pressure and leveraging the competitive suppression of resistant cancer cells by their sensitive counterparts, thereby delaying the emergence of resistance (39,42).

The core hypothesis of adaptive therapy is that intrinsic competition exists between drug-sensitive and drug-resistant cancer cells within the tumor microenvironment (25,77-79). Conventional high-dose continuous therapy [e.g., daily EGFR-tyrosine kinase inhibitor (TKI) or fixed-schedule chemotherapy], while rapidly reducing tumor volume, simultaneously eliminates the ecological suppression of resistant cells by sensitive cells, leading to the rapid expansion of resistant clones (25,42). By contrast, adaptive therapy employs dynamically adjusted treatment regimens (including dose reduction or treatment holidays) intended to maintain a population of sensitive cells, thereby continuously suppressing the proliferation advantage of resistant subclones. Mathematical modeling has demonstrated the potential of this strategy to markedly prolong the disease control period (39,78). Its implementation relies on two key elements: i) Reliable biomarkers for the real-time assessment of tumor burden and clonal composition; and ii) Pre-defined decision algorithms to guide treatment adjustments. ctDNA sequencing therefore provides an ideal tool for this purpose; longitudinal monitoring of specific mutant allele frequencies allows quantification of the relative proportions of different clones, establishing a data-driven basis for therapeutic intervention (9,28,80).

Preclinical models and clinical studies have demonstrated notable advantages for adaptive therapy (42,81,82). For instance, in animal models, dynamically adjusting chemotherapy regimens based on drug sensitivity testing results markedly extended survival compared with standard fixed-dose regimens (42). Clinical evidence also supports the feasibility of ctDNA-guided adaptive therapy in NSCLC. In a non-randomized controlled trial of 60 patients with advanced NSCLC who achieved complete remission after targeted therapy and local consolidative treatment, Dong *et al* (81) reported a median progression-free survival of 18.4 months using a ctDNA-guided adaptive de-escalation TKI strategy. Notably, 23% of patients required no further TKI treatment and 52% received intermittent TKI retreatment based on ctDNA or CEA levels before radiographic progression, suggesting that ctDNA serves as a reliable trigger for treatment re-initiation (81). Thus, this strategy may be clinically feasible in a subset of patients with advanced NSCLC. Real-world data from Noronha *et al* (82) further demonstrated that reduced-frequency osimertinib dosing is a viable alternative for patients unable to tolerate full-dose daily therapy, supporting individualized dose modulation. Collectively, these studies provide initial clinical proof-of-concept that biomarker-driven adaptive therapy can prolong disease control and potentially reduce treatment burden and toxicity.

Table I. Comparison of emerging therapeutic strategies targeting spatiotemporal heterogeneity in non-small cell lung cancer.

| Strategy | Core principle | Representative methods and targets | Advantages | Challenges |
|---|---|---|---|---|
| Evolutionary trap therapy | Guides tumor clones toward a drug-sensitive or less fit state | Sequential/alternating therapy, low-dose metronomic chemotherapy | May delay resistance and enhance subsequent treatment efficacy | Difficult to predict evolutionary trajectories; complex regimen design |
| Niche intervention | Targets the tumor microenvironment to indirectly control cancer | Examples include CSF-1R, CCR2/CCR5 and TGF-β inhibitors | Potentially broad suppression of heterogeneous clones; durable effect | Limited target specificity; risk of off-target effects |
| Adaptive therapy | Utilizes competitive suppression to maintain a stable sensitive cell population | ctDNA-guided dose adjustment algorithms | Aims for long-term disease control; potentially reduced toxicity | Requires accurate predictive models and real-time monitoring |

ctDNA, circulating tumor DNA; CSF-1R, colony-stimulating Factor 1 receptor; CCR, C-C chemokine receptor.

The ongoing Canadian Cancer Trials Group BR.36 trial (trial ID: NCT04767061) is prospectively evaluating ctDNA molecular response-adaptive immuno-chemotherapy in metastatic NSCLC. Its first stage validated the feasibility of ctDNA-based response monitoring, demonstrating that early ctDNA dynamics can guide treatment adjustment (83). This trial exemplifies the integration of ctDNA kinetics into adaptive immunotherapy regimens. The primary challenges facing adaptive therapy include developing accurate predictive models, determining optimal thresholds for treatment adjustment and addressing complexities introduced by tumor clonal plasticity. Furthermore, this personalized, dynamic treatment model poses new requirements for traditional clinical trial design and regulatory approval frameworks. By viewing cancer as a dynamic evolutionary system and intervening using ecological principles, adaptive therapy offers a promising new avenue for achieving long-term control in NSCLC. With advancements in precision monitoring technologies (such as longitudinal ctDNA and spatial multi-omics) and computational biology (including AI-driven evolutionary modeling), this strategy is poised to become an important component in addressing tumor heterogeneity and drug resistance. Table I summarizes the comparison of emerging treatment strategies targeting spatiotemporal heterogeneity in NSCLC.

Furthermore, to translate dynamic management into practice, the present review proposes a ctDNA-based algorithm (Fig. 2) outlining baseline assessment, monitoring frequency (week 4, then every 8-12 weeks), response thresholds (≥50% variant allele frequency decrease), warning signals (≥2X increase or resistance mutation) and management of progression or discordant findings.

## 4. Challenges and future perspectives

Despite the marked promise of novel therapeutic strategies based on spatiotemporal heterogeneity, their clinical translation faces numerous challenges. Technically, the application of spatial multi-omics technologies is still limited by high technical barriers, complex data analysis and a lack of standardization; the detection sensitivity of liquid biopsy in patients with early-stage tumors or low tumor burden requires further improvement. Biologically, the phenotypic plasticity of tumor cells and non-genetic resistance mechanisms increase the complexity of predicting clonal evolution. From a clinical translation perspective, dynamic treatment strategies pose transformative demands on traditional clinical trial designs, efficacy evaluation criteria and regulatory approval frameworks.

Beyond biological and technical complexities, clinical translation faces multiple practical barriers. Cost-effectiveness remains a concern, as spatial multi-omics and liquid biopsy are still expensive with limited reimbursement coverage. Turnaround time for spatial omics (1-2 weeks) and liquid biopsy (7-14 days) may exceed the decision window for rapidly progressive NSCLC. Accessibility differs notably between academic centers and community hospitals, exacerbating healthcare disparities (84). Regarding standardization, data comparability across different platforms (such as 10x vs. Vizgen) (85) and ctDNA assays remains poor. International consortia (including SpaceTx; https://spacetx-starfish.readthedocs.io/) are working on advancing benchmarking and quality control, yet widespread clinical harmonization remains a future goal. Overcoming these barriers is important in translating the dynamic management paradigm into real-world NSCLC care.

Future research efforts should thus focus on the following key areas: i) Innovating clinical trial paradigms: Promoting the adoption of adaptive designs, such as platform and umbrella trials, as mainstream approaches and establishing endpoint indicators and statistical models suitable for evaluating dynamic therapies; ii) deep integration of multi-omics data: Leveraging artificial intelligence and machine learning algorithms to integrate multidimensional information from genomics, transcriptomics and the microenvironment for

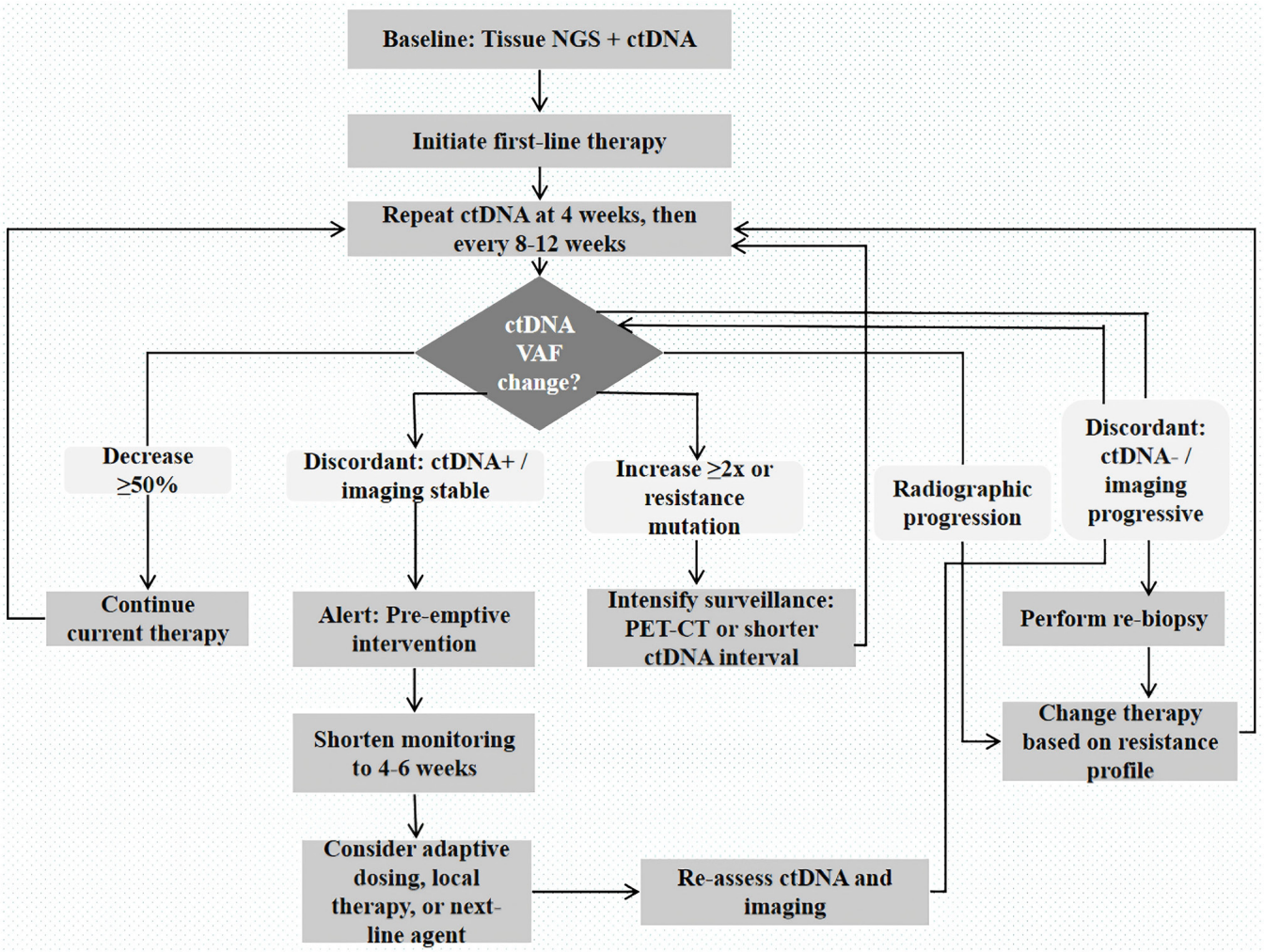


Figure 2. ctDNA-guided dynamic management algorithm for advanced NSCLC. Flowchart integrating ctDNA dynamics, imaging and clinical data to enable early intervention before radiographic progression. This algorithm is intended for patients with advanced (stage IIIB-IV) NSCLC and Eastern Cooperative Oncology Group performance status 0-2, receiving first-line systemic therapy. ctDNA, circulating tumor DNA; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; VAF, variant allele frequency.

constructing high-precision predictive models of clonal evolution; iii) optimizing dynamic treatment strategies: Exploring the synergistic effects of different treatment modalities with adaptive dosing and establishing individualized treatment algorithms based on real-time biomarker feedback; and iv) promoting technical standardization and accessibility: Reducing the costs of multi-omics technologies, establishing standardized data analysis pipelines and facilitating their widespread clinical adoption.

In summary, overcoming the challenge of spatiotemporal heterogeneity in NSCLC necessitates surmounting technical bottlenecks, deepening biological understanding and innovating clinical practice models. Through multidisciplinary collaborative innovation, the paradigm shift in NSCLC management, from reactive response to proactive control, can ultimately be realized.

## 5. Conclusion

Spatiotemporal heterogeneity is an intrinsic property of NSCLC as a dynamic evolutionary system and constitutes a key reason for the limitations of current treatment paradigms. Overcoming this bottleneck necessitates a paradigm shift: froma static, molecular-subtyping-driven approach towards a dynamic, evolution-focused strategy that emphasizes continuous monitoring and adaptive intervention. Advanced technologies have provided us with the initial capability to map the spatiotemporal atlas of NSCLC. Emerging strategies, such as evolutionary trap therapy, niche intervention and adaptive therapy, offer promising directions for transitioning the treatment goal from ‘eradication’ to ‘intelligent management’. Future success will therefore depend on the integration of tumor biology, evolutionary ecology, computational science and clinical medicine, with the ultimate objective being to transform NSCLC into a chronic disease that can be controlled long-term.

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## Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

LC contributed to the conceptualization, design, analysis and writing of the original and subsequent drafts. WZ was responsible for interpretation of the data and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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