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Review Article

Spatial Tumor Heterogeneity: The Next Frontier in Understanding Cancer Resistance

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Abstract:

Spatial tumour heterogeneity, which denotes the changes in cellular and molecular attributes across distinct locations within a tumour, significantly influences cancer diagnosis and treatment resistance. The heterogeneity of tumour cells inside a singular mass facilitates tumour development, metastasis, and the ineffectiveness of standard therapy. Comprehending the geographical distribution of tumour cells is crucial for formulating more efficient treatment regimens. Diverse methodologies are employed to investigate spatial heterogeneity, encompassing modern imaging techniques such as MRI, PET, and multiplexed imaging, alongside omics approaches including genomes, transcriptomics, and proteomics. These instruments offer insights into the tumour microenvironment and facilitate the identification of resistant subpopulations. The amalgamation of imaging and genomic data via radiogenomics has emerged as a viable methodology, providing an extensive perspective on the spatial and molecular intricacies of tumours. Principal findings reveal that spatial heterogeneity fosters medication resistance by establishing microenvironments characterised by varying oxygen levels, immunological infiltration, and genetic alterations, hence complicating the efficacy of monotherapy strategies. Hypoxic environments and immunological evasion significantly contribute to treatment resistance. Addressing geographical heterogeneity has the potential to enhance cancer treatments. By analysing the molecular and geographical characteristics of tumours, physicians can customise therapies more efficiently, minimising resistance and improving therapeutic results. This methodology signifies a vital advancement in precision medicine, providing more individualised and efficacious cancer therapies in the future.

Keywords: Spatial Tumor Heterogeneity; Cancer Resistance; Imaging Techniques; Radiogenomics; Drug Resistance; Precision Medicine; Tumor Microenvironment; Hypoxia; Immune Evasion; Multiplexed Imaging; Genomics; Proteomics

Introduction

Cancer heterogeneity is a defining characteristic of tumour biology, significantly impacting cancer diagnosis, prognosis, and treatment. Tumour heterogeneity denotes the existence of genetic and phenotypic variation within an individual tumour, significantly influencing the progression, metastasis, and therapeutic resistance of cancers. This complexity can be classified into two primary categories: genetic and geographic heterogeneity [1]. Genetic heterogeneity denotes the variations in the genetic composition of tumour cells, frequently influenced by mutations, amplifications, and deletions. Spatial heterogeneity denotes the variability in tumour features throughout distinct parts of the tumour microenvironment (TME) and is increasingly acknowledged for its significant influence on cancer biology [2]. The spatial organisation of cancer cells within the tumour is regulated by genetic variables as well as microenvironmental elements, including hypoxia, nutrition gradients, and immune cell infiltration. This spatial heterogeneity represents a novel frontier in cancer research, as it affects tumour behaviour and therapy response in ways that are just starting to be comprehended [3].

Spatial heterogeneity inside tumours is becoming recognised as a vital element in cancer treatment. It denotes the heterogeneous dispersion of tumour cells within a singular tumour mass, characterised by different microenvironments that differ in molecular composition, metabolic status, and treatment susceptibility [4]. In contrast to genetic alterations, which are frequently identifiable via biopsy or sequencing, spatial heterogeneity necessitates sophisticated imaging and multi-omics methodologies to elucidate its intricacies. This comprehension has significant ramifications for precision medicine, wherein treatments are customised to the unique molecular characteristics of a patient's tumour [5]. Through the analysis of geographical distribution, physicians may effectively identify certain tumour locations exhibiting greater resistance to medicines, thus enhancing treatment efficacy and reducing the likelihood of relapse. Notwithstanding its increasing significance, the influence of spatial tumour heterogeneity on cancer resistance continues to provide a considerable challenge. Conventional diagnostic methods, mostly centred on bulk tumour specimens or single-site biopsies, frequently neglect to encompass the complete intricacy of spatial heterogeneity [6]. Consequently, these techniques may neglect essential subpopulations of resistant cells that could contribute to treatment failure. The absence of thorough methodologies for in vivo evaluation of tumour heterogeneity and the incapacity to dynamically monitor tumour response to therapy in real-time constitute significant constraints in contemporary cancer treatment frameworks. These problems highlight the necessity for research aimed at comprehending the spatial organisation of tumours and their contribution to resistance mechanisms [7].

This research seeks to investigate the nascent domain of spatial tumour heterogeneity and its role in cancer resistance. By examining the intricate relationship between geographical heterogeneity and therapeutic resistance, we aim to identify existing research gaps and suggest solutions to address these issues [8]. This review will illustrate how spatial heterogeneity, through an examination of recent advancements in imaging, omics technologies, and radiogenomics, might enhance the precision of therapy regimens for cancer patients. This work seeks to deliver a thorough examination of the potential of spatial tumour heterogeneity as a diagnostic instrument and therapeutic target in combating cancer. *Figure 1 provides a visual representation of spatial tumor heterogeneity, illustrating the diverse regions within a tumor that contribute to its resistance mechanisms and therapeutic challenges* [9].

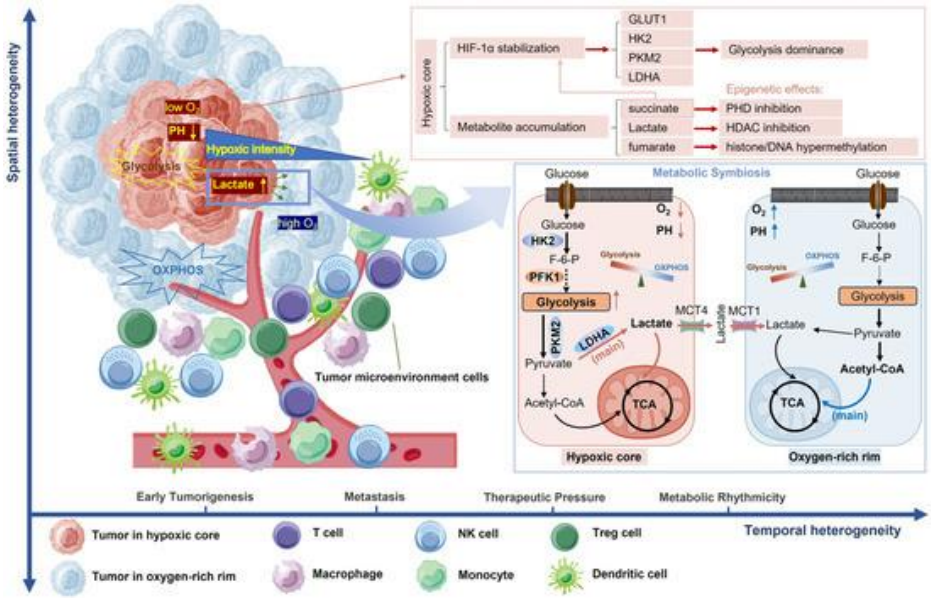

Fig 1: Spatiotemporal Heterogeneity of Tumor Glucose Metabolism Reprogramming: From Single-Cell Mechanisms to Precision Interventions. This fig delves into the dynamic reprogramming of glucose metabolism in tumors, emphasizing the importance of spatial and temporal heterogeneity. Advancements in single-cell sequencing, spatial omics, and metabolic imaging have shifted the paradigm from static analyses to high-resolution investigations of metabolic variations at the single-cell level. The article explores how these metabolic shifts influence tumor progression and response to therapies, highlighting the role of the glucose metabolism–epigenetics–immunology regulatory axis. By integrating these insights, the authors propose strategies for developing targeted interventions that address the complexities of tumor metabolism.

Summary of key points. Spatial tumor heterogeneity—differences in cell clones, perfusion, and immune contexture across regions—reliably predicts why some pockets resist therapy. We synthesize evidence across imaging, spatial-omics, and radiogenomics showing how these patterns map to hypoxia, immune exclusion, and drug delivery barriers. We outline practical workflows that convert those signals into decision-ready reports for tumor boards. Finally, we identify the main translational hurdles (standardization, validation, cost, and regulatory) and propose near-term solutions

The Role of Spatial Tumor Heterogeneity in Cancer Progression

Tumor Microenvironment (TME)

The tumour microenvironment (TME) is pivotal in the emergence of geographic heterogeneity in tumours. The tumour microenvironment (TME) comprises a complex network of cells, extracellular matrix constituents, blood arteries, and signalling chemicals that encircle and engage with tumour cells. This microenvironment is heterogeneous, differing both within various parts of the same tumour and among distinct tumours. Spatial heterogeneity emerges from the complex interactions among these tumour microenvironment components, which affect the tumor's biological behaviour and its treatment response [10].

A significant element influencing regional heterogeneity in the tumour microenvironment is hypoxia. Tumours frequently surpass their vascular supply, resulting in areas of hypoxia inside the tumour mass. Hypoxic areas, commonly situated near the tumor's centre, are generally marked by heightened resistance to chemotherapy and radiotherapy. Hypoxia activates multiple molecular pathways, notably the hypoxia-inducible factor (HIF) pathway, which facilitates tumour cell survival in oxygen-deficient regions by boosting angiogenesis, glycolysis, and various metabolic alterations. Besides hypoxia, immune cells in the tumour microenvironment contribute to geographic heterogeneity [11]. Immune cells, including T cells, macrophages, and dendritic cells, enter distinct tumour areas at varied densities. The presence and function of immune cells are frequently affected by the tumor's spatial design, which can either facilitate or impede tumor progression. The vasculature significantly influences the geographic heterogeneity of the tumour microenvironment (TME). The atypical blood arteries supplying tumours are generally permeable and chaotic, leading to inconsistent blood flow and the formation of areas with varying nutrition and oxygen concentrations. The disordered vasculature results in the development of

inadequately perfused regions, which contribute to the tumor's overall heterogeneity [12].

Clonal Evolution

Spatial heterogeneity is both a result of the tumour microenvironment and a catalyst for clonal evolution in cancer. Clonal evolution denotes the process through which tumour cells accumulate genetic changes over time, resulting in the formation of genetically different subpopulations, or clones, within an individual tumour. These clones have differing levels of aggressiveness, metastatic capability, and resistance to therapy, with their spatial distribution controlled by internal factors (e.g., genetic alterations) and extrinsic factors (e.g., the tumour microenvironment) [13].

Spatial heterogeneity promotes clonal evolution by creating diverse habitats inside the tumour, each characterised by unique selective pressures. Regions of the tumour subjected to elevated oxidative stress, hypoxia, or immune cell infiltration may promote the survival of clones more adeptly suited to these environments. This selection pressure propels the evolution of clones possessing genetic alterations that bestow resistance to treatments or facilitate metastasis. Research indicates that genetic heterogeneity within tumours correlates with poorer prognosis and more aggressive disease progression. In breast cancer, the existence of several genetically different clones inside a single tumour is associated with heightened metastatic potential and inferior patient outcomes. In glioblastoma, clonal evolution exacerbates the tumor's heterogeneity, complicating effective treatment. In these tumours, areas with elevated genetic alterations frequently exhibit greater resistance to standard therapies, whereas more genetically stable regions are less aggressive but may nonetheless play a role in tumour recurrence [14].

Intercellular Interactions

The interactions among various tumour cell types within the spatial environment additionally affect tumour growth and therapeutic resistance. These interactions are very dynamic, regulated by direct cell-to-cell contact and the production of soluble molecules that modify the behaviour of adjacent cells. In a tumour, peripheral cells may communicate with core cells via signalling molecules such as cytokines and growth factors, resulting in a heterogeneous tumour mass with diverse phenotypic traits. Intercellular interactions can enhance resistance mechanisms by fostering a more conducive milieu for specific cell populations [15].

The epithelial-mesenchymal transition (EMT) is a crucial signalling mechanism affected by geographical differences. Epithelial-mesenchymal transition (EMT) is a process whereby epithelial cells obtain mesenchymal traits, facilitating their migration and invasion into adjacent tissues. This mechanism is frequently linked to tumour advancement and metastasis. In tumours exhibiting spatial heterogeneity, epithelial-mesenchymal transition (EMT) is not equally active throughout all regions [16]. Cells in hypoxic or inadequately perfused regions may demonstrate a more pronounced epithelial-mesenchymal transition (EMT) phenotype, facilitating their invasion into adjacent tissues and the formation of secondary tumours. The PI3K/AKT pathway, which governs cell survival, proliferation, and metabolism, is significantly influenced by geographical heterogeneity. In select areas of the tumour, particularly those exhibiting elevated cellular density or distinct extracellular matrix constituents, PI3K/AKT signalling may be more intense, enhancing cell survival and facilitating resistance to apoptosis. The Wnt signalling pathway, integral to cell proliferation and differentiation, significantly contributes to tumour growth. In spatially heterogeneous tumours, the activation of the Wnt pathway may differ among various tumour locations, affecting tumour cell behaviour and contributing to resistance mechanisms [17].

The interplay between tumour cells and their microenvironment is additionally influenced by stromal cells, including cancer-associated fibroblasts (CAFs), which release extracellular matrix constituents and growth factors. These stromal cells establish a physical and metabolic barrier that affects drug distribution and the efficacy of treatments. In some areas of the tumour, cancer-associated fibroblasts (CAFs) may assist tumour cells in evading immune surveillance or augment the resistance of tumour cells to chemotherapeutic agents [18].

Spatial heterogeneity significantly influences tumour behaviour and treatment response. Spatial heterogeneity influences clonal evolution, intercellular connections, and signalling pathways, hence contributing to cancer growth, aggressiveness, and resistance, which is crucial for comprehending tumour biology and enhancing therapeutic options.

Mechanisms of Cancer Resistance Linked to Spatial Heterogeneity

Drug Resistance

Spatial heterogeneity significantly influences the emergence of treatment resistance in tumours. This resistance is not solely due to genetic changes but is frequently intensified by the spatial arrangement of tumour cells inside the tumour microenvironment (TME). Distinct tumour locations may have varied sensitivity to chemotherapy and targeted therapies,

mostly attributable to variations in oxygen availability, nutritional concentrations, cellular density, and the presence of stromal cells. In areas of the tumour characterised by significant hypoxia or inadequate nutritional availability, cells frequently experience heightened metabolic stress and demonstrate modified drug absorption, metabolism, and efflux, rendering them less vulnerable to standard therapies [19].

An illustrative instance of this phenomenon is evident in treatment resistance in solid tumours. In numerous malignancies, including glioblastoma and non-small cell lung cancer (NSCLC), the core hypoxic areas of the tumour demonstrate resistance to chemotherapy due to compromised drug delivery, modified cellular metabolism, and increased efflux pump activity. P-glycoprotein (P-gp), a membrane-associated transporter protein, is frequently increased in hypoxic areas, facilitating the efflux of chemotherapy agents such as doxorubicin, hence diminishing their efficacy [20].

Additionally, spatially disparate areas of the tumour may include genetically heterogeneous clones, each exhibiting different resistance profiles. In breast cancer, research indicates that the tumour periphery, characterised by superior oxygenation and vascularization, typically demonstrates a more favourable response to therapy, whereas the core displays increased resistance attributed to the hypoxic microenvironment and modified expression of drug-metabolizing enzymes. This varied medication sensitivity highlights the necessity for more advanced treatment techniques that consider the geographical heterogeneity within tumours. In targeted therapies, geographical heterogeneity can complicate treatment outcomes because of tumour subpopulations with unique genetic profiles. In HER2-positive breast cancer, tumour cells in hypoxic regions may downregulate HER2 expression, resulting in diminished responsiveness to HER2-targeted therapy such as trastuzumab [21]. These geographically different subpopulations can circumvent treatment by modifying critical signalling pathways or by acquiring mutations in therapeutic targets. *Figure 2 provides a conceptual overview of the various mechanisms contributing to drug resistance in different regions of the tumor, including hypoxia-driven resistance, immune evasion, and the emergence of resistant subclones* [22].

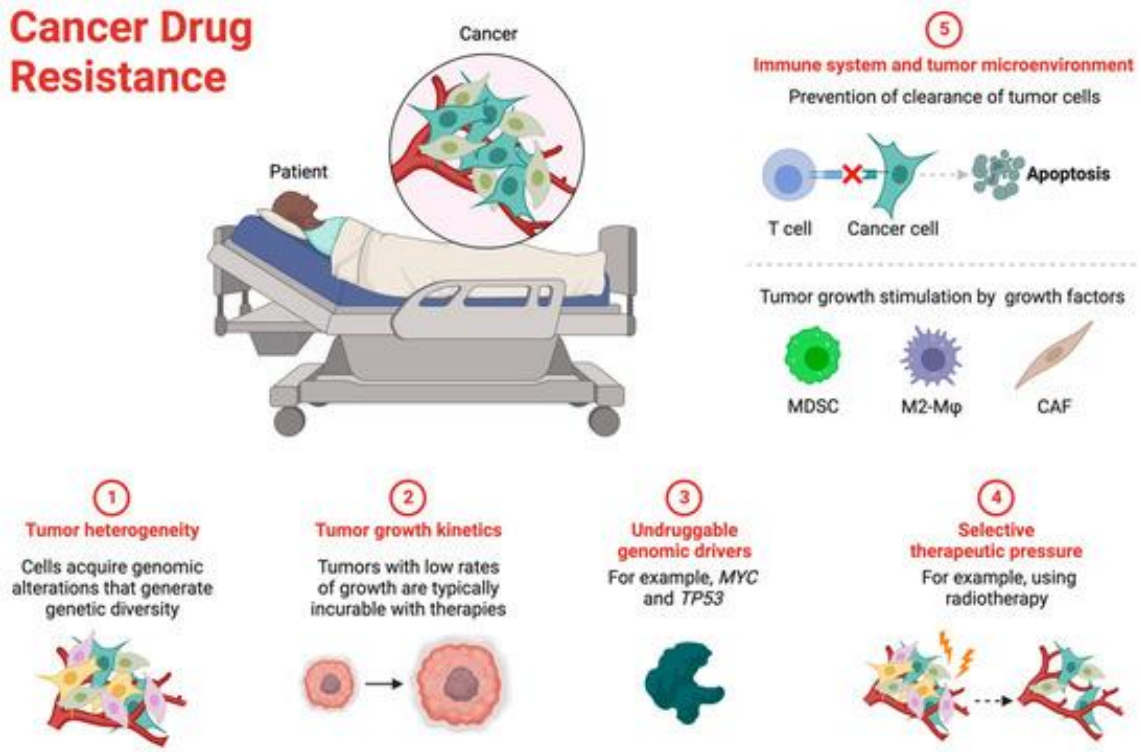

Fig 2: Multilevel Mechanisms of Cancer Drug Resistance. This figure explores the complex factors contributing to cancer drug resistance, including tumor heterogeneity, cancer stem cells, and the tumor microenvironment. It discusses how somatic mutations within tumors, enhanced DNA repair capabilities of stem cells, and interactions with immune cells and fibroblasts complicate treatment. Additionally, the article highlights how selective therapeutic pressures, such as radiotherapy, can induce resistance. The review emphasizes the need for combination therapies to overcome these multifaceted challenges in cancer treatment.

Immune Resistance

Spatial heterogeneity significantly influences immune resistance, since distinct tumour areas may display differing levels of immune cell infiltration and expression of immune checkpoint molecules. Immune surveillance, essential for identifying and eradicating tumour cells, may be hindered by the tumor's spatial layout, resulting in immune evasion in specific tumour locations. In numerous solid tumours, the immunological "cold" patches are characterised by restricted immune cell infiltration, typically located in the tumor's core. These regions are deficient in essential immune cells, including T cells, dendritic cells, and macrophages, required for a successful immunological response. Conversely, the immunological "hot" areas in the tumour perimeter frequently exhibit elevated levels of immune cell infiltration. Nonetheless, even in these immunodense regions, tumour cells can circumvent immune responses by upregulating immune checkpoint molecules such as PD-L1 (programmed death-ligand 1). These chemicals engage with their receptors on T cells (e.g., PD-1), resulting in T-cell fatigue and the inhibition of immunological responses. Immune checkpoint inhibitors are typically higher expressed in the peripheral layers of tumours, where immune cells are more prevalent, hence contributing to immune resistance in these areas [19,23].

An exemplary case of immune resistance associated with spatial heterogeneity is shown in melanoma, wherein immune checkpoint drugs such as anti-PD-1 treatment have demonstrated considerable therapeutic efficacy. Nonetheless, these medicines exhibit diminished efficacy in tumours characterised by diverse immune infiltration. Tumours characterised by areas lacking immune cells (cold tumours) demonstrate less responsiveness to immunotherapy, while places with increased immune infiltration (hot tumours) may show enhanced efficacy. Moreover, tumours exhibiting geographic heterogeneity might attract immunosuppressive cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), to specific areas, therefore further attenuating the immune response [24].

The capacity of tumours to circumvent immune surveillance in particular areas not only affects the efficacy of immunotherapy but also challenges the advancement of more effective immunotherapeutic strategies. Addressing geographically diverse immune evasion mechanisms may be essential to improve the overall efficacy of immunotherapy.

Therapeutic Implications

Comprehending spatial heterogeneity in tumours presents novel opportunities for enhancing cancer treatments, especially in addressing the obstacles of drug and immune resistance. A potential technique involves localised therapies that target the delivery of elevated medication concentrations or therapeutic agents directly to specific tumour areas. This can address the challenge of inadequate medication penetration in hypoxic or crowded tumour regions. Locally administered chemotherapies or nanoparticle-based drug delivery systems may offer tailored treatment for resistant tumour areas, enhancing therapeutic efficacy and reducing systemic adverse effects [25].

Another potential approach is combination therapy, which seeks to simultaneously address many facets of tumour resistance. Combining chemotherapy with immune checkpoint inhibitors may mitigate the resistance mechanisms in immunosuppressive tumour areas. Likewise, integrating targeted medicines that concentrate on certain biochemical pathways, such as PI3K inhibitors with HER2-targeted therapies, may effectively tackle the genetic and geographic heterogeneity of the tumour. Novel therapies also utilise tumor-stromal interactions to alter the tumour microenvironment. Stromal-modifying drugs that target cancer-associated fibroblasts (CAFs) or extracellular matrix components may affect the spatial configuration of tumour cells, hence enhancing their vulnerability to chemotherapy or immunological response. Moreover, techniques designed to reconfigure the tumour vasculature, including vascular normalisation therapy, may enhance the supply of chemotherapeutic drugs and immune cells to inadequately perfused tumour areas, hence improving treatment efficacy [26,27].

The emergence of spatial transcriptomics and radiogenomics enables the utilisation of spatial data from tumours to develop medicines specifically customised to the tumor's architecture. This data-centric methodology facilitates the creation of individualised treatment protocols that consider both the genetic and geographical characteristics of a patient's tumour, yielding a more accurate and efficacious therapeutic approach.

Comprehending the significance of spatial variation in cancer resistance offers a means to address substantial obstacles in cancer treatment. By focusing on spatially distinct tumour locations with localised therapies, integrating treatments, and employing breakthrough technology, we can more effectively tackle the intricate and evolving nature of tumour resistance, hence enhancing patient outcomes [28].

Techniques for Studying Spatial Tumor Heterogeneity

Imaging Techniques

Improvements in imaging tools have greatly enhanced our comprehension of spatial tumour heterogeneity, allowing researchers to observe the complex variations within tumour areas and their adjacent microenvironment. Conventional imaging techniques, including magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT) scans, have historically been utilised to examine tumour architecture and functionality. These imaging techniques offer macroscopic insights into tumour dimensions, morphology, and metabolic activity. MRI is extensively utilised to assess tissue architecture and the geographic distribution of tumour areas, especially beneficial for brain and soft tissue malignancies. PET and CT scans, although they provide insights into tumour metabolic activity and blood flow, exhibit insufficient resolution on detailed spatial heterogeneity at the cellular level [29].

Although conventional approaches yield significant insights, they are constrained in their ability to uncover cellular and molecular heterogeneities inside the tumour. In response, advanced imaging techniques have developed, facilitating enhanced resolution and more intricate visualisation of tumour heterogeneity. Multiplexed imaging facilitates the concurrent identification of many molecular targets inside tissue specimens, offering an extensive perspective of the tumor's spatial structure. This methodology integrates many imaging techniques, including immunofluorescence and mass spectrometry, to concurrently visualise various biomolecules inside a single tissue section, thereby providing insights into the heterogeneity of molecular markers, immune cell infiltration, and extracellular matrix constituents. Three-dimensional imaging is an advanced technique that produces three-dimensional reconstructions of tumour tissues, enabling researchers to examine the spatial arrangement of cells within the tumour with greater precision. Intravital microscopy is an advanced technology that facilitates the real-time observation of living tumour cells within intact tissues, offering a dynamic perspective on tumour progression, cellular migration, and therapeutic responses in their natural context. These sophisticated imaging techniques are essential for comprehending the influence of spatial heterogeneity on tumour proliferation and therapeutic resistance [30].

Omics Approaches

Besides imaging techniques, omics methodologies have emerged as crucial instruments for investigating spatial tumour heterogeneity. These methods amalgamate extensive molecular data, including genomic, transcriptomic, and proteomic information, to investigate the intricate interactions between tumour cells and their microenvironment. Genomic study reveals mutations, copy number variations, and chromosomal rearrangements that lead to tumour heterogeneity. When integrated with spatial data, genomic methodologies can identify certain tumour locations containing more aggressive or resistant clones [31].

Transcriptomics elucidates gene expression profiles across various tumour areas, emphasising the impact of cellular spatial distribution on their functional states. Single-cell RNA sequencing (scRNA-seq) is an innovative technique that facilitates the analysis of gene expression at the individual cell level. This approach can identify subpopulations of cells with unique transcriptional fingerprints, highlighting cellular diversity across various tumour areas. Single-cell RNA sequencing has demonstrated significant use in identifying unusual cell types that contribute to therapeutic resistance and metastasis [32]. Spatial transcriptomics is an emerging discipline that integrates gene expression profiling with spatial data, facilitating the mapping of gene activity inside tissue slices while maintaining the tissue's geographical context. This technique facilitates a high-resolution, localised examination of the molecular heterogeneity of tumours, elucidating the relationships between discrete tumour areas and their milieu, as well as the implications of these interactions for cancer growth and resistance [33].

Proteomics facilitates the examination of protein expression and alterations, yielding a functional assessment of the molecular processes occurring within various tumour areas. This method can assist in identifying resistance biomarkers and signalling pathways that are variably active in different tumour regions. Integrating proteomics with geographical data enables researchers to achieve a comprehensive understanding of the protein networks that regulate tumour heterogeneity and resistance mechanisms [34].

Computational Models

Computational models have become increasingly essential for analysing the extensive data produced by imaging and omics approaches in the investigation of spatial tumour heterogeneity. These models facilitate the amalgamation of many data kinds and offer robust instruments for forecasting tumour behaviour and therapy responses. One of the most sophisticated techniques is the creation of spatially resolved tumour atlases, which are comprehensive maps of tumours at the molecular, cellular, and tissue

levels. These atlases integrate spatial transcriptomics, imaging, and histology data to establish a complete reference for investigating tumour growth, resistance, and heterogeneity across many cancer types [35].

Machine learning algorithms are utilised to forecast tumour behaviour based on spatial heterogeneity. These models can amalgamate data from imaging, genetics, and proteomics to categorise tumour areas, anticipate therapy responses, and project clinical outcomes. Machine learning, by training algorithms on extensive datasets, can discern patterns that may not be immediately evident through conventional analysis, so facilitating more precise predictions of tumour responses to various therapies. This is especially beneficial in personalised medicine, where therapies can be customised to the unique spatial and molecular attributes of a patient's tumour [36].

Moreover, agent-based modelling and computational fluid dynamics are employed to mimic the dynamics of tumour proliferation, angiogenesis, and pharmacological administration in spatially heterogeneous tumours. These models integrate elements like as oxygen gradients, immune cell migration, and extracellular matrix reorganisation, offering insights into how these elements affect the tumor's spatial structure and its therapeutic response.

Collectively, these computational methods foster a more refined comprehension of spatial heterogeneity, hence aiding in the formulation of personalised treatment regimens aimed at specific tumour areas or biological pathways. By integrating computer models with experimental data, researchers can create dynamic, predictive models of tumour behaviour, thereby improving the creation of more effective and targeted medicines [37].

The integration of modern imaging techniques, omics methodologies, and computational models is facilitating substantial advancements in our comprehension of spatial tumour heterogeneity. These approaches offer critical instruments for identifying tumour subpopulations, elucidating resistance mechanisms, and formulating personalised treatment plans. As these technologies advance, they possess the capacity to transform cancer diagnosis, treatment, and prognosis, ultimately resulting in more efficacious medicines for patients [5].

Radiogenomics: Linking Spatial Heterogeneity with Imaging and Genomic Data

Definition of Radiogenomics

Radiogenomics is a nascent interdisciplinary domain that integrates radiomics (image-derived biomarkers) with genomic information to improve our comprehension of cancer at molecular and spatial dimensions. Radiogenomics seeks to combine sophisticated imaging methods with genetic data to discern tumour attributes that may be undetected by either approach independently. Radiogenomics has the potential to transform cancer diagnosis by providing a more thorough understanding of tumour heterogeneity, encompassing both genetic composition and geographic distribution of tumour cells. This data integration facilitates the mapping of genetic characteristics to distinct tumour locations, elucidating the impact of spatial heterogeneity on cancer growth and therapeutic response [38].

The principal benefit of radiogenomics in cancer detection is its capacity to offer a non-invasive method for finding and monitoring tumour heterogeneity. Conventional genomic analysis necessitates biopsy samples; however, imaging modalities like MRI, CT, PET, and multiplexed imaging can offer real-time insights into tumour architecture and metabolic activity without invasive procedures. Integrating genomic data with imaging modalities enables clinicians to examine the molecular foundations of spatial heterogeneity and perhaps forecast the treatment response of specific tumour locations, so providing a more accurate cancer management strategy [39]. *As shown in Figure 3, the integration of radiomic features from imaging data with genomic profiles provides a more comprehensive understanding of spatial tumor heterogeneity, allowing for better prediction of therapy response and resistance mechanisms* [40].

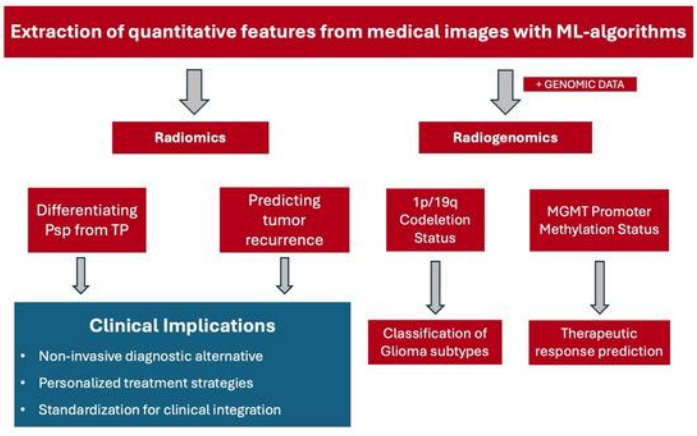

Fig 3: The Process of Radiomics and Radiogenomics in Comparison to Conventional Imaging Methods. This diagram visually represents the workflow involved in radiomics and radiogenomics methodologies, starting from image acquisition to diagnosis or clinical outcomes. It illustrates how the process integrates various data types, including genomic and omics data, after the initial image segmentation and data extraction. The comparison with

conventional imaging highlights the additional layer of genomic data integration in radiogenomics for a more comprehensive clinical assessment

Radiomics and Genomic Data Integration

The amalgamation of radiomics and genomic data facilitates the detection of regional patterns of tumour resistance that may remain undetected when utilising either modality in isolation. Radiomics entails the extraction of quantitative characteristics from medical imaging, including texture, shape, and intensity, which represent the underlying tumour microenvironment and its heterogeneity. These characteristics are essential in delineating tumour regions with varying biological behaviours, including locations exhibiting heightened vascularity, hypoxia, or cellular density. By linking these image-based traits with genomic data, researchers might obtain profound insights into the molecular foundations of tumour heterogeneity and resistance mechanisms [41].

Numerous studies have shown that radiomics can aid in identifying spatial patterns linked to medication resistance. In non-small cell lung cancer (NSCLC), radiomic characteristics such as tumour texture and morphology have been associated with distinct genetic subgroups, including those containing EGFR or KRAS mutations. These genetic modifications are frequently linked to specific resistance patterns to targeted medicines [42]. Zhang et al. (2024) showed that radiomic characteristics derived from CT scans of lung cancer patients correlate with molecular subtypes, offering significant predictive insights into therapy response and prognosis. Breast cancer research indicates that radiomic characteristics derived from MRI scans can forecast HER2 overexpression and other genetic markers, which correlate with certain therapeutic responses, such as to trastuzumab [43].

These investigations underscore the efficacy of integrating radiomic data with genetic information to pinpoint tumour locations that may contain resistant subpopulations. Besides genetic mutations, radiomics can elucidate alterations in the tumour microenvironment that foster resistance, including the formation of hypoxic regions or immune evasion niches. These locations may have unique radiomic signals that, when combined with genetic data, yield a more precise prediction of the therapeutic response of various tumour sites [38].

Clinical Applications

The clinical implementation of radiogenomics demonstrates significant potential in enhancing cancer treatment techniques, especially in predicting therapeutic responses and personalising treatment regimens. Radiogenomics is primarily utilised to forecast tumour responses to various treatments, such as chemotherapy, radiation therapy, and immunotherapy. By amalgamating radiomic characteristics with genomic data, doctors might discern tumours that are predisposed to respond to specific therapies based on their molecular profile and spatial heterogeneity [40].

Radiogenomics can predict the probability of tumour recurrence or metastasis by identifying tumour areas that exhibit greater treatment resistance. In glioblastoma, a highly heterogeneous and aggressive malignancy, radiogenomic methodologies have been employed to forecast the tumor's response to radiation therapy by correlating radiomic characteristics (such as tumour morphology and texture) with distinct molecular indicators, including MGMT promoter methylation status. Patients with tumours resistant to radiation can be identified early, facilitating more precise therapies, such as the administration of temozolomide or alternative chemotherapeutic drugs [44].

Radiogenomics is essential in formulating personalised treatment strategies. By integrating the geographical and molecular attributes of a patient's tumour, physicians can formulate more efficacious and personalised therapy. Radiogenomics can inform the selection of immunotherapies for tumours characterised by elevated immune checkpoint markers or distinct patterns of immune cell infiltration. By combining immune-related characteristics with genetic data, doctors can more accurately predict which patients are likely to benefit from immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors, hence avoiding ineffective treatments [44].

Moreover, radiogenomics possesses the capacity to enhance the assessment of therapy response. Therapeutic interventions allow for the monitoring of alterations in the tumor's molecular profile and geographic heterogeneity using successive imaging and genomic assessments. This facilitates real-time evaluation of therapy efficacy and may provide chances for early intervention upon detection of resistance. In ovarian cancer, radiogenomics has been employed to monitor alterations in the tumor's radiomic characteristics and molecular markers in response to chemotherapy, offering insights into the temporal evolution of various tumour locations.

In conclusion, radiogenomics presents an innovative methodology for cancer detection and treatment by amalgamating imaging and genomic data to elucidate the intricate geographic heterogeneity of tumours. This comprehensive approach offers significant insights into tumour resistance processes and has the potential to enhance therapy prediction, tailor treatment strategies, and assess therapeutic

response. As technologies progress, the capacity of radiogenomics to revolutionise cancer treatment will expand, providing patients with more accurate and efficacious therapeutic alternatives [45].

Future Directions and Challenges

Technological Advancements

The examination of spatial tumour heterogeneity is set for substantial advancement as new technologies progress. The urgent requirement is for the advancement of imaging techniques that provide enhanced resolution and greater penetration into tumour tissues. Contemporary imaging modalities such as MRI, CT, and PET scans offer significant insights; nonetheless, they frequently fall short in their capacity to delineate tumour microstructures at the cellular or molecular scale [46]. Advanced imaging technologies, like multiplexed imaging and 3D imaging, are enhancing spatial resolution; however, additional improvements are necessary to achieve more granular data. High-resolution intravital microscopy techniques offer potential for in vivo investigations by enabling real-time visualisation of tumour processes. Furthermore, the incorporation of these imaging modalities with data integration systems that amalgamate imaging, genomic, and proteomic data in real time will be crucial for comprehensively comprehending spatial heterogeneity and its influence on cancer progression and resistance.

Artificial intelligence (AI) is anticipated to be essential in the future of tumour spatial analysis. AI-driven algorithms can analyse extensive imaging and omics data to uncover concealed patterns and forecast tumour behaviour with greater precision. Utilising machine learning and deep learning methodologies, AI can improve picture spatial resolution, autonomously segment tumours, and associate spatial characteristics with molecular fingerprints, resulting in more accurate identification of tumour subpopulations and prediction of treatment efficacy. AI can aid in the creation of predictive models for tumour growth and therapeutic resistance, facilitating more targeted and individualised treatment strategies [47,48].

Challenges

Notwithstanding the promise of these technological breakthroughs, considerable technical obstacles persist in the acquisition and analysis of the intricate data related to spatial tumour heterogeneity. Tumours demonstrate significant complexity and variability, complicating the comprehensive capture of geographic heterogeneity through any singular technique. The amalgamation of varied data types, including imaging, genomics, and proteomics, constitutes a significant challenge, as each modality possesses distinct limits and necessitates advanced computational methods for integration [49].

The interpretation of data presents an additional challenge in the examination of spatial variability. Due to the substantial amount of data produced by imaging and omics approaches, standardisation challenges frequently occur in data analysis and interpretation. Inconsistencies in the methodologies employed for data collection, processing, and analysis can result in divergent outcomes, complicating the capacity to formulate universal conclusions or identify dependable biomarkers. Establishing standardised processes for data gathering and processing is essential for ensuring reproducibility and enabling multi-center investigations [50].

Clinical Translation

Despite considerable advancements in the laboratory, the application of these discoveries in clinical practice continues to pose difficulties. The clinical application of spatial tumour heterogeneity research necessitates the creation of more accessible and standardised diagnostic instruments suitable for widespread use in medical environments. Surmounting the financial and temporal obstacles linked to these new technologies is essential, as numerous existing approaches are resource-intensive and may not be practical for regular clinical application. Nonetheless, substantial potential exists for enhancing patient outcomes by addressing geographic variation in forthcoming medicines. By comprehending the responses of various tumour sites to treatment, clinicians can more effectively pinpoint spots necessitating intensified therapy or those with an elevated risk of recurrence. Customised treatment protocols that incorporate spatial heterogeneity may result in more efficacious cancer therapies with fewer adverse effects. Moreover, spatially-targeted therapies, including localised drug delivery and immunotherapy strategies aimed at resistant tumour areas, present significant opportunities for surmounting resistance and enhancing overall survival rates [51,52].

Despite the hurdles in technology and clinical translation, the future of investigating spatial tumour heterogeneity is highly promising. With the emergence of new technologies and an enhanced comprehension of tumour complexity, these improvements are expected to yield more accurate and effective cancer medicines, hence enhancing patient outcomes and transforming cancer care.

Future work should move beyond technology descriptions to **decision-changing evidence**. Priority

studies include prospective, habitat-guided biopsy trials (does imaging truly find discordant/resistant clones?), adaptive protocols that trigger early therapy switches based on week-3/6 imaging "habitat" response, and multi-site external validations with locked, IBSI-aligned pipelines to ensure calibration and reproducibility. Coupled, co-registered spatial omics can biologically validate what radiogenomic "habitats" mean, while pragmatic cost-effectiveness and equity audits (across scanners, sites, and demographics) will determine whether these approaches are affordable and fair at scale.

Conclusion

What can be integrated now (0–6 months).

1. **Standardize inputs:** adopt brief protocol cards for CT/MRI/PET (voxel size, kernel, normalization) and document segmentation with inter-reader agreement.
2. **Start with triage radiogenomics:** deploy a locked, IBSI-aligned feature set to flag hypoxia-like, immune-excluded, and high-cellularity "habitats" from routine scans—no new hardware required.
3. **Make it decision-ready:** generate a **one-page report** (habitats, suggested biopsy targets, therapy implications, trial flags) for tumor boards.
4. **Measure what matters:** track simple KPIs—time-to-treatment-switch, percentage of "non-diagnostic" biopsies avoided, and concordance with pathology.

Build reliability and scale (6–18 months).

5. **Prospective pilot(s):** pre-register a multi-site evaluation with fixed thresholds and calibration reporting; use decision-relevant endpoints (early progression under neoadjuvant therapy, time-to-switch).
6. **Selective spatial assays:** use imaging as a **triage** to decide *who* needs multiplex/spatial-omics and *where* to sample, reducing cost while increasing yield.
7. **Governance & transparency:** publish a brief model card (intended use, population, failure modes) and keep a version-locked pipeline for clinical evaluation.
8. **Training & handoff:** provide a 30-minute tumor-board walkthrough (how to read habitat maps; when to escalate or switch) and a checklist embedded in the report [53].

Health-system readiness.

These steps leverage existing PACS and pathology pipelines, require minimal additional staff time once templates are set, and focus investment where it changes decisions—biopsy targeting, early escalation, and rational combinations.

Limitations and next steps.

Harmonization across scanners, external validation, and reimbursement pathways remain essential. We recommend community adoption of IBSI-aligned features, shared reference datasets, and reporting standards that emphasize calibration and net clinical benefit.

Take-home.

By pairing standardized imaging with streamlined reporting and targeted confirmation assays, centers can begin using spatial heterogeneity within the next year to make earlier, better-informed decisions—bringing precision oncology closer to real-time practice [54].

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