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The metastatic journey and the uniqueness of the pulmonary system

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Abstract:

The lungs are among the most frequent sites of distant dissemination of malignancy, a phenomenon driven by the organ's unique physiological properties and complex molecular interactions. This paper provides a comprehensive review of the biological mechanisms underlying pulmonary metastasis and explores their direct implications for surgical management, specifically pulmonary metastasectomy (PM). The metastatic journey is analyzed through the lens of three evolving models of tumorigenesis: the stochastic model, the cancer stem cell model, and the cellular plasticity model. Central to this dissemination is the epithelial-mesenchymal transition (EMT), a dynamic process in which tumor cells acquire a hybrid phenotype that facilitates invasion, intravasation, and immune evasion. The lung's susceptibility is attributed to its receipt of the entire cardiac output, its dense capillary network, and its establishment of pre-metastatic niches. These niches, modulated by inflammatory responses and extracellular matrix remodeling, create a permissive microenvironment for disseminated tumor cells (DTCs) to undergo colonization or to enter states of dormancy. Clinically, the efficacy of PM is rooted in these biological realities. The necessity for radical R0 resection and systematic lymphadenectomy is supported by routes of hematogenous and lymphatic spread. Furthermore, the debate between traditional thoracotomy and minimally invasive surgery (MIS) is framed by the biological challenge of radiologically occult nodules that may require bimanual palpation for identification. A comparative perspective on colorectal carcinoma, renal cell carcinoma, sarcomas, and germ cell tumors illustrates how histological behavior dictates surgical timing and the integration of systemic therapies. While advances in immunotherapy and molecular targeting offer hope, the heterogeneity of metastatic disease and the protective nature of the pulmonary microenvironment remain significant barriers. This review underscores that future therapeutic success necessitates a multidisciplinary approach targeting both tumor-intrinsic drivers and extrinsic niche factors. Ultimately, a deeper synthesis of metastasis biology and surgical principles is essential to refine therapeutic algorithms and improve long-term survival for patients with secondary pulmonary malignancies.

Keywords:

Epithelial-mesenchymal transition, metastasectomy, pre-metastatic niche, pulmonary metastasis, thoracic surgery, tumor biology

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Introduction

The lungs are among the most common destinations for metastatic spread. Pulmonary metastases frequently arise from extrapulmonary sites due to hematogenous, lymphatic, or transcoelomic spread.[1–3] It is commonly accepted that circulating tumor cells enter the lungs via the venous circulation and are trapped in the pulmonary parenchyma due to the filtering function of the lungs. This idea is complex and, for most clinicians, often difficult to comprehend. The process involves a dynamic and complex sequence in which healthy cells are transformed into cancerous cells, leading to uncontrolled proliferation, immune evasion, resistance to programmed cell death, promotion of angiogenesis, acquisition of invasive capabilities, survival in the bloodstream, and the establishment of malignant growths in distant organs [Fig. 1].[4–8] This paper seeks to clarify the metastatic journey by concentrating on the complex processes of primary tumor formation and metastasis and by examining how distinct characteristics of the pulmonary system lead to a greater prevalence of metastases than in other body regions, thereby aiding clinicians' understanding of the fundamental mechanisms underlying metastasis.

Pulmonary Metastases and Metastasectomy

Approximately 30% of patients diagnosed with a malignancy will eventually develop pulmonary metastases. These secondary lesions frequently originate from carcinomas of the colon and rectum, kidney, breast, prostate, and oropharynx. Furthermore, certain tumors such as choriocarcinoma, osteosarcoma, soft tissue sarcoma, testicular germ cell tumors, Ewing sarcoma, and thyroid carcinoma exhibit a preferential metastatic affinity for the lungs. Pulmonary metastasectomy has emerged as a well-established therapeutic intervention that substantially improves long-term survival for patients with lung metastases from solid tumors, and currently represents a significant proportion of the clinical workload in thoracic surgery departments. The pillars of this surgical approach include radical resection to ensure negative surgical margins and adequate lymphadenectomy. The primary objective is to achieve complete resection of all metastatic foci while maximizing the preservation of the lung parenchyma. Consequently, while limited resections, primarily wedge resections, are the standard treatment for peripheral lesions, centrally located tumors may require anatomical resections such as segmentectomy or lobectomy and, in exceptionally rare cases, pneumonectomy.[9]

Surgical indications are determined through a case-specific evaluation by a multidisciplinary team. The conventional criteria for intervention include the effective control of the primary malignancy, the absence of extrapulmonary metastatic disease, and the technical feasibility of achieving a complete resection of all pulmonary lesions. Additionally, the patient must be a suitable surgical candidate with an acceptable risk profile and preserved physiological reserve. While the presence of multiple metastases is not an absolute contraindication, having three or more nodules is recognized as a significant prognostic factor that may increase the risk of mortality by 33%. Nonetheless, surgi-

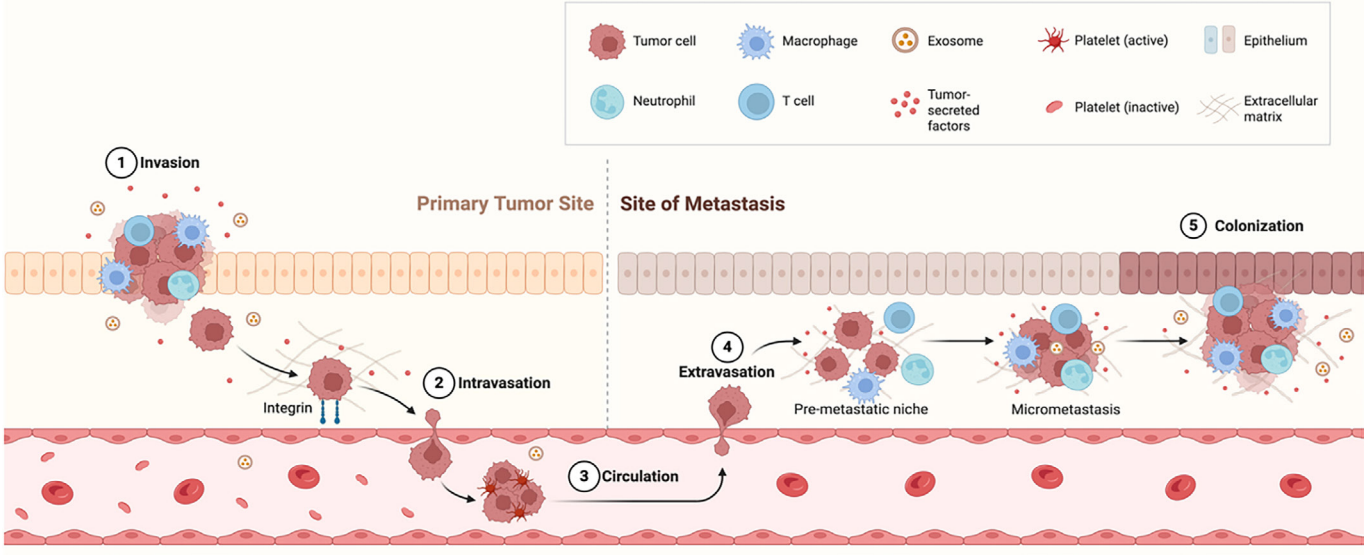

Figure 1: Overview of metastatic cascade

cal intervention should remain a viable consideration for appropriate patients presenting with two to four lesions.[10]

The optimal surgical approach, comparing traditional thoracotomy with minimally invasive surgery (MIS), remains subject to debate. Thoracotomy provides the advantage of bimanual palpation of the entire lung, facilitating the identification of occult nodules not detected by preoperative imaging, which occurs in 18% to 36% of cases according to various studies.[11,12] Conversely, MIS is often the preferred modality for medically eligible patients due to its association with shorter recovery periods, fewer postoperative complications, and superior quality of life. MIS is particularly beneficial in reducing pleural adhesions, an important consideration for patients who may require subsequent metastasectomies.

Maintaining an adequate surgical margin is essential to reduce the risk of local recurrence, particularly in wedge resections. Current evidence recommends a surgical margin of more than 10 mm and a tumor size-to-margin ratio of less than 1.7. Furthermore, because intrathoracic lymph node (LN) involvement is a poor prognostic indicator, routine LN sampling or formal dissection is recommended during the procedure. Finally, an aggressive surgical approach, including redo surgery for recurrent metastases, is justified under similar clinical indications when complete resection is feasible and the patient maintains adequate functional status.[9]

The surgical strategies and prognostic considerations outlined above underscore the clinical complexity of managing secondary pulmonary lesions. However, the efficacy of these interventions is fundamentally rooted in the biological behavior of the primary malignancy. Understanding the mechanisms of tumorigenesis and the pathways of metastasis facilitates a comprehensive grasp of the disease, thereby enabling the more precise formulation of therapeutic algorithms. In this context, determining the surgical modality for metastasectomy, for example, whether to include lymph node dissection, is of paramount clinical importance. Consequently, a deeper exploration into the molecular drivers of primary tumor development and the intricate biological cascades that govern metastatic dissemination is essential to further refine these surgical paradigms.

Formation of the Primary Tumor

Numerous factors, including chemically driven carcinogenesis, viral infections, changes in epigenetic patterns, and somatic mutations, contribute to cancer development. Our present understanding of how healthy cells are converted into cancerous ones is guided by three distinct models [Fig. 2].[13]

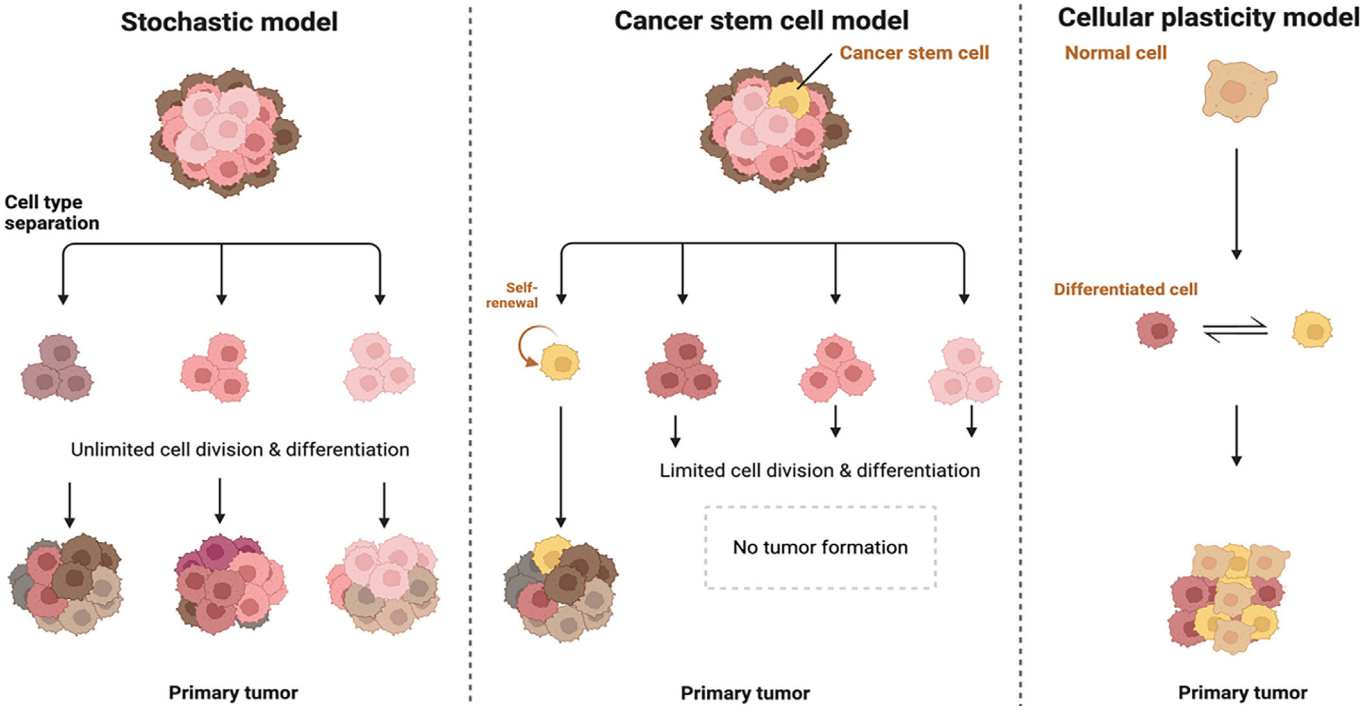

Figure 2: Schematic illustration for the models of tumorigenesis

The stochastic tumorigenesis model suggests that cancer arises due to random genetic mutations and alterations that accumulate in normal cells over time. This model assumes that every cell in the body has some probability of developing cancer-causing mutations; essentially, it treats cancer development as a matter of chance. The key features of the stochastic model are:

- **Random Mutations:** In this model, the genetic mutations that lead to cancer are unexpected events that can occur during cell division or DNA replication, or in response to environmental factors such as radiation or chemicals. These mutations can affect genes responsible for cell cycle regulation, DNA repair, and other critical cellular processes.
- **No Specific Cell Type:** In contrast to the cancer stem cell model, the stochastic model does not posit a distinct stem-like cell population; rather, it proposes that any normal cell may acquire oncogenic mutations and undergo malignant transformation.
- **Gradual Progression:** Tumorigenesis in the stochastic model is gradual and progressive. A single cell accumulates multiple mutations over time, eventually leading to uncontrolled cell growth and tumor development.
- **Heterogeneity:** Tumors formed under the stochastic model often exhibit genetic and phenotypic heterogeneity, as the mutations can vary between individual cancer cells within the same tumor.[14,15]

Conversely, the cancer stem cell (CSC) model postulates that tumor growth and progression are driven by a small subpopulation of stem-like cells capable of self-renewal and differentiation into diverse cancer cell lineages. The key characteristics of this model include:

- **Hierarchical Organization:** The CSC model suggests that tumors are hierarchically organized, with a small population of CSCs at the apex. CSCs can divide to produce more CSCs (self-renewal) and can differentiate into non-CSC cancer cells that constitute the bulk of the tumor.
- **Specific Cell Type:** Unlike the stochastic model, the CSC model posits the existence of specific cells (CSCs) that initiate and sustain tumorigenesis. These cells are believed to be more resistant to conventional cancer treatments, such as chemotherapy and radiation therapy.
- **Tumor Heterogeneity:** This model also accounts for the genetic and phenotypic heterogeneity of tumors. Differentiated cancer cells within the tumor are derived from CSCs and may have varying degrees of genetic mutations and aggressiveness.
- **Target for Therapy:** The CSC model suggests that targeting and eliminating CSCs should be a priority in cancer therapy, as they are the driving force behind tumor growth and recurrence. Developing treatments that specifically target CSCs is an ongoing area of research.[16]

The recently proposed cellular plasticity model challenges the traditional cancer stem cell (CSC) paradigm by positing that CSCs do not arise from a fixed cell of origin. Instead, it suggests that normal cells possess intrinsic plasticity, enabling epigenetic and phenotypic reprogramming in response to internal or external stimuli. This plasticity facilitates the acquisition of CSC characteristics and contributes to mutational accumulation and intratumoral heterogeneity.[17] These models are not mutually exclusive, and individual tumors may exhibit features of both to varying extents. Tumorigenesis is therefore a heterogeneous and multifactorial process, differing across cancer types and patients, and remains an active area of oncologic investigation.[18]

Molecular Biology of Metastasis

Cancer metastasis, the dissemination of malignant cells from a primary tumor to distant organs, remains a major challenge in oncology, with fewer than 0.01% of primary tumor cells ultimately forming macrometastases at secondary sites.[19] Clinically established organ-specific metastasis models demonstrate that metastatic organ tropism is nonrandom and is strongly influenced by the microenvironment of secondary sites.[20]

The timing at which a primary tumor acquires metastatic potential remains poorly defined. Although metastatic dissemination was traditionally attributed to microenvironmental stresses such as hypoxia and nutrient deprivation, emerging evidence in HER2-positive breast cancer indicates that tumor cell dissemination may occur prior to clinical detectability of the primary lesion, with circulating tumor cells capable of seeding distant metastases.[21,22] The detection of circulating tumor cells prior to clinical identification of a primary tumor challenges conventional models of metastasis. Among metastatic sites, the lung is the most frequently involved, underscoring

the need to elucidate the molecular mechanisms governing pulmonary metastasis to advance cancer biology and inform targeted therapeutic strategies.[23]

Formation of the Pre-metastatic Niche: Central to the process of lung metastasis is the formation of a specific microenvironment known as the premetastatic niche. This tissue-specific niche is created by genetic mutations and epigenetic changes in primary tumor cells and promotes altered intercellular communication among cell types.[24] Additionally, the release of signaling mediators such as cytokines, chemokines, exosomes, and growth factors enhances microenvironmental responses, creating a favorable environment for metastatic cells.[25]

Epithelial-Mesenchymal Transition (EMT): Epithelial–mesenchymal transition (EMT) is a key mechanism in lung metastasis, whereby cancer cells lose epithelial characteristics and acquire mesenchymal traits, resulting in increased motility and invasiveness. This process is regulated by transcription factors including Snail, Slug, Twist, and ZEB1.[26] Only a subset of cancer cells can intravasate and survive within the circulation; successful metastasis requires the acquisition of stem cell–like properties and invasive capabilities.[27] This transformation is mediated by epithelial–mesenchymal transition (EMT), characterized by loss of epithelial polarity and cell–cell junctions with concurrent acquisition of mesenchymal migratory and invasive properties.[28,29] During EMT, a subset of cells adopts a hybrid epithelial/mesenchymal (E/M) phenotype, co-expressing epithelial and mesenchymal markers. These cells retain limited cell–cell adhesion mediated by E- and N-cadherin, albeit weaker than in fully epithelial cells. In contrast, cells with a predominantly mesenchymal phenotype, key drivers of metastasis, exhibit actin and vimentin-rich cytoskeletal structures that enhance migratory and invasive capacities.[30] Complete mesenchymal transition is not required for metastatic competence; instead, a hybrid epithelial/mesenchymal (E/M) state is pivotal. EMT constitutes a reversible phenotypic continuum, in which mesenchymal traits promote invasion, whereas metastatic colonization often requires epithelial reversion via mesenchymal–epithelial transition (MET).[31,32] Cells exhibiting EMT-MET plasticity can undergo EMT or MET and adapt to changes in the microenvironment. Furthermore, hypotheses suggest that cells with EMT-MET plasticity have a higher potential for tumor initiation and metastasis than cells at either end of the EMT spectrum.[33]

The hybrid epithelial/mesenchymal(E/M) phenotype is associated with enhanced metastatic capacity, increased tumor-initiating potential, therapeutic resistance, and poor prognosis, and is linked to resistance to antiestrogen therapies and elevated programmed death-ligand 1(PD-L1)expression.[34,35] Cells undergoing partial EMT adopt an intermediate phenotype, co-express epithelial and mesenchymal traits, and often migrate collectively while retaining cell–cell adhesions. Figure 3 illustrates the EMT spectrum, which varies *in vivo* according to tissue context, epithelial differentiation, junctional organization, basal adhesion, and EMT regulatory mechanisms.[36]

Hybrid epithelial/mesenchymal (E/M) cells promote an immunosuppressive microenvironment by recruiting myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated M2 macrophages (TAMs) through secretion of cytokines and chemokines, including IL-8.[37] These immunoregulatory effects are further amplified by impaired caspase-dependent apoptosis and reduced antigen-presenting capacity, both of which are characteristic features of hybrid epithelial/mesenchymal (E/M) cells.

Extracellular Matrix Reconstruction and Vascular Invasion: Metastatic cells must penetrate the extracellular matrix(ECM)to invade neighboring tissues and blood vessels. Matrix metalloproteinases(MMPs)play an essential role in ECM remodeling. These enzymes are regulated by various signaling pathways, such as TGF-β.[38] Cancer cells undergoing EMT enter the bloodstream via intravasation with the help of cell surface adhesion molecules such as integrins and selectins. Signaling pathways such as PI3K/AKT and MAPK contribute to the invasion process.[39]

Primary tumor cells may enter the circulation either as single cells or through collective migration, processes that differ in cellular morphology and underlying molecular mechanisms. Regardless of the invasion mode, dissemination enables tumor cells to detach from the primary site and intravasate into the bloodstream. Emerging anti-invasive strategies target cytoskeletal components, such as vimentin, to disrupt intermediate filament assembly; altered vimentin phosphorylation impairs cellular mechanical properties. However, further investigation is required to determine whether targeting intermediate filaments can effectively inhibit metastatic progression.[40]

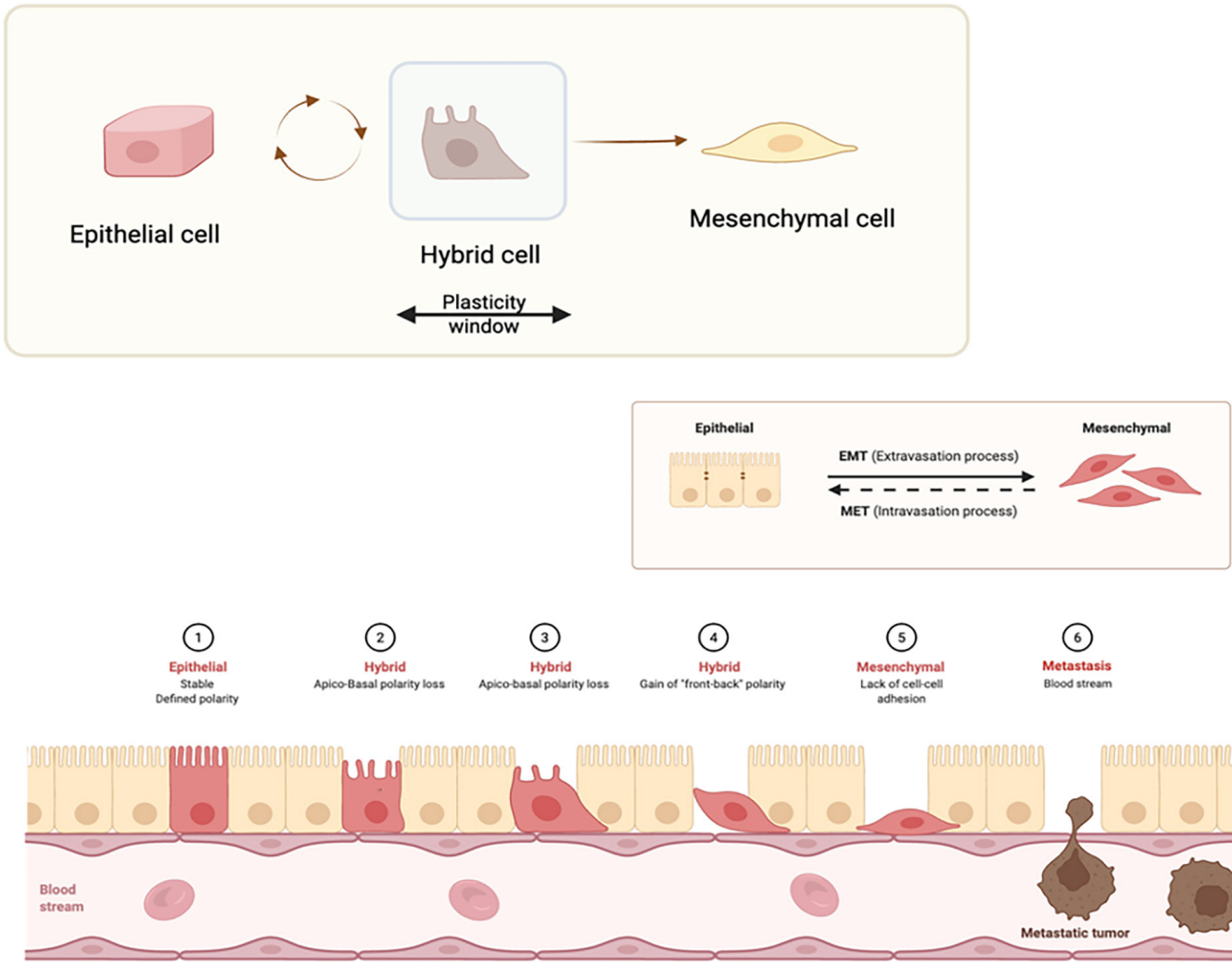

Figure 3: EMT (epithelial-mesenchymal transition) and MET (mesenchymal-epithelial transition). EMT and MET orchestrate dynamic and reversible changes involving a range of intermediate epithelial-mesenchymal phenotypes. Fully developed epithelial cells are characterized by apical-basal polarity, lateral cell-cell connections such as adherens junctions, gap junctions, tight junctions, and connections to the basement membrane. In contrast, mesenchymal cells exhibit anteroposterior polarity, lack cell-cell adhesion and move independently when detached from the basement membrane

Intravasation and Immune Modulation: Following intravasation, most circulating tumor cells are eliminated by hemodynamic shear stress and immune surveillance; fewer than 0.01% successfully extravasate at distant sites. Vascular invasion may occur via active or passive mechanisms; in passive invasion, the majority of cells undergo apoptosis. This attrition has been attributed to unfavorable microenvironmental conditions, including hypoxia-induced nutrient deprivation and the structurally leaky nature of tumor-associated vasculature.[41,42]

Conversely, during active intravasation, cells utilize the process of chemotaxis to migrate toward blood vessels, controlled by gradients of nutrients and growth factors.[43] These cells degrade the ECM and basement membrane and actively invade blood vessels via intravasation. These cancer cells form bonds with platelets as they circulate, allowing them to withstand shear stress.[42,43]

Arrest and Extravasation: To establish metastatic lesions, cancer cells must undergo extravasation, a multistep process involving endothelial adhesion at secondary sites, disruption of the endothelial barrier, and transendothelial migration into surrounding tissues.[44] During circulation, cancer cells are mechanically arrested within pulmonary microvessels before migrating into the lung parenchyma, a process mediated by adhesion molecules including ICAM-1, VCAM-1, and E-selectin, as well as chemokines and cytokines such as CXCL12 and IL-8.[45]

Immune Modulation: Cancer cells evade immune-mediated destruction through multiple mechanisms, including the creation of an immunosuppressive microenvironment via secretion of soluble factors such as VEGF, IL-10, TGF-β, prostaglandin E_2, and Fas ligand. Additionally, downregulation of antigen-presenting machinery, particularly the expression of the major histocompatibility complex (MHC), enables escape from immune surveillance. Circulating tumor cells may also be shielded by platelet cloaking, which protects them from T-cell and natural killer cell–mediated cytotoxicity, while platelet-to-tumor transfer of MHC molecules further contributes to immune evasion.[17] Moreover, during multiple stages of T-cell activation, the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death-1/programmed death-ligand 1(PD-1/PD-L1) immune checkpoint pathways negatively regulate T-cell function, thereby fostering an immunosuppressive microenvironment and promoting tumor progression.

PD-1/PD-L1–mediated immune evasion is primarily driven by tumor PD-L1 overexpression, which engages PD-1 on activated T cells and inhibits PI3K/AKT and Ras/MEK/ERK signaling, while CTLA-4 binding to CD80/CD86 suppresses costimulatory signals essential for T-cell activation and proliferation.[46]

Angiogenesis: Angiogenesis represents a principal route of tumor dissemination, as newly formed tumor-associated vessels are structurally abnormal, exhibiting hyperplasia, excessive branching, and increased permeability. These defects facilitate vascular leakage and enable tumor cells to escape from the primary tumor.[47] Primary tumors remain localized while the angiogenic switch is inactive; its delayed activation, occurring months to years after tumor initiation, reactivates tumor growth, sustains proliferation, and enables dissemination to secondary sites. Accordingly, clinically quiescent tumors or micrometastases may persist in a dormant state until angiogenesis is triggered.[48]

In addition to hematogenous spread, cancer cells may disseminate via lymphatic and perineural routes. Lymphatic spread typically involves initial seeding of regional lymph nodes followed by distant organ metastasis, a process critically regulated by factors such as vascular endothelial growth factor (VEGF) and angiopoietin-2.[14,49] Overexpression of VEGF-C or VEGF-D promotes tumor-associated lymphangiogenesis, thereby facilitating cancer cell dissemination.[50] Perineural dissemination involves tumor spread along neural axons and the surrounding perineural sheath and has been documented in multiple malignancies, including breast, pancreatic, prostate, colorectal, and head and neck cancers.[51] Perineural spread is initiated within a specialized peripheral microenvironment composed of neural cells, inflammatory infiltrates, extracellular matrix, vasculature, and immune components, which collectively facilitate metastatic progression.[52]

Dormancy in Micrometastasis: Following extravasation, many disseminated cancer cells fail to develop into macrometastases and instead persist as solitary cells or small micrometastatic clusters that enter a state of quiescence. Metastatic dormancy is characterized by cell cycle arrest and may result from inadequate growth factor signaling, activation of metastasis suppressor genes (cytostatic dormancy), failure to initiate angiogenesis (angiogenic dormancy), or sustained immune-mediated control (immunologic dormancy).[53–55] Cell-cycle arrest represents a double-edged strategy, as quiescence may render conventional therapies, particularly those targeting rapidly proliferating cells, ineffective. Dormant micrometastatic cells may either persist in quiescence or re-enter active proliferation. Although modulation of pathways such as AXL/Gas6 can induce dormancy, the durability of this suppression is uncertain. Accordingly, strategies that promote dormancy and prevent macrometastatic outgrowth primarily delay disease progression rather than provide curative benefit.[56]

What Makes the Pulmonary System Unique?

The lung is the most common site of metastasis, owing to the distinctive features of the pulmonary system. It receives the entire cardiac output, contains the densest capillary network in the body, and represents the first capillary bed encountered by much of the lymphatic drainage before venous return. In addition, its extensive network of thin alveolar–capillary membranes readily traps circulating tumor cells. Collectively, these characteristics create a permissive microenvironment for metastatic seeding and growth in the lung.[57] Although several metastatic routes to the lung exist, hematogenous dissemination is the predominant pathway. The growth of pulmonary metastases depends on an adequate blood supply, and the lung's dual circulatory system, pulmonary and bronchial, acting independently or in combination, provides a vascular milieu that may facilitate metastatic establishment and progression.[58,59]

Multiple malignancies, including breast, melanoma, and colorectal cancers, release soluble factors and extracellular vesicles that remodel the pulmonary microenvironment and establish pre-metastatic niches. Murine models show that these niches, marked by immune and inflammatory cell recruitment, organ-specific chemoattractants, growth factors, and extracellular matrix remodeling, create permissive conditions for tumor cell extravasation, colonization, and metastatic outgrowth.[60,61]

After entering the circulation, disseminated tumor cells (DTCs) extravasate through the pulmonary endothelium into the lung parenchyma, where pre-metastatic niche mechanisms support colonization. Hypoxia-induced lysyl oxidases promote collagen crosslinking, enhancing myeloid cell adhesion and niche formation. In parallel, chemokines released by alveolar type II cells recruit neutrophils that facilitate colonization of leukotriene B4 receptor 2 (LTB4R2)–positive DTCs, suppress $CD8^+$ T-cell activation, and promote metastatic outgrowth through secretion of cathepsin G and neutrophil elastase, which degrade the tumor-suppressive factor thrombospondin-1 (TSP1).[62–64]

After colonization, disseminated tumor cells (DTCs) adapt to the pulmonary microenvironment with support from α4 integrin–expressing macrophages, which activate pro-survival AKT signaling. Metastatic outgrowth is further promoted by angiogenesis driven by bone marrow–derived endothelial progenitor cells or by VEGF-induced VEGFR2 activation in the lung endothelium. Although natural killer (NK) cells are central to tumor immunosurveillance, hypoxia-driven CCL2 secretion recruits granulocytic myeloid cells, thereby establishing an immunosuppressive niche that impairs NK cell maturation and cytotoxicity.[60]

Pre-existing pulmonary inflammation, such as that induced by cigarette smoke exposure, may further facilitate metastasis. Inflammatory mechanisms implicated in this process include activation of the ubiquitin–CXCR4 axis, upregulation of E-selectin in lung tissue, NF-κB activation in airway epithelial cells, increased CCL2 expression, and enhanced macrophage infiltration within the pulmonary microenvironment.[65,66]

Further studies are needed to clarify the complex interactions between the host microenvironment, immune system, and lung structure that could also impact prognosis and therapeutic approaches.[67]

Clinical Implications of Metastasis Biology: The Underlying Mechanisms at the Core of Metastasectomy

The physiological and molecular characteristics of the pulmonary system render it a highly permissive environment for metastatic seeding, primarily due to its dense capillary network and role as the first major capillary bed for lymphatic and venous return. Beyond simple mechanical trapping of tumor cells, the lung actively facilitates colonization through the establishment of pre-metastatic niches. These niches, driven by soluble factors, extracellular matrix remodeling, and the recruitment of immunosuppressive myeloid cells, suppress anti-tumor immunity(such as NK-cell and $CD8^+$ T-cell activity)and promote pro-survival signaling. Furthermore, the lung's dual circulatory system and inflammatory triggers, including cigarette smoke, exacerbate this susceptibility by enhancing vascularization and chemoattractant expression.[24,25,31,32]

From a clinical perspective, these biological mechanisms provide a profound rationale for the surgical principles of pulmonary metastasectomy. The predominantly hematogenous pathway of dissemination explains the necessity for radical and complete resection of all detectable nodules to achieve oncological control. The involvement of the lymphatic system and recruitment of inflammatory cells into the lung parenchyma underscore the paramount importance of lymph node dissection and sampling, since intrathoracic lymph node involvement directly indicates systemic disease progression and poor prognosis. Moreover, the recognition that the pulmonary microenvironment can harbor radiologically occult disseminated tumor cells (DTCs) justifies the surgical debate between thoracotomy and MIS, in which bimanual palpation may be required to address the biological reality of multifocal seeding. Ultimately, the transition from tumor biology to surgical intervention reflects a comprehensive strategy to disrupt the permissive milieu and improve patient prognosis through precise anatomical and oncological clearance.

Clinical Application of Pulmonary Metastasectomy

The clinical application of pulmonary metastasectomy is fundamentally dictated by the interplay between tumor histology and the receptive biology of the lung. In contemporary thoracic practice, PM is most frequently indicated for colorectal carcinomas, sarcomas (both soft-tissue

sarcomas and osteosarcomas), renal cell carcinomas, and selected head-and-neck tumors or germ-cell tumors. These malignancies typically exhibit a focal colonization pattern, in which disseminated tumor cells (DTCs) utilize the lung's dense capillary network for mechanical entrapment but remain relatively localized within the parenchyma. For these patients, surgical intervention serves as a critical tool to physically disrupt the pro-survival AKT signaling and angiogenic support provided by the pulmonary microenvironment, offering substantial long-term survival benefits that systemic therapies alone may not achieve.[41–43]

In contrast, certain secondary pulmonary malignancies are traditionally excluded from surgical consideration due to their distinct biological behavior or extreme sensitivity to systemic agents. Hematological malignancies (e.g., Hodgkin and non-Hodgkin lymphomas) and highly chemosensitive tumors, such as small-cell lung cancer, are managed with systemic therapies because their diffuse molecular signaling renders local surgical excision ineffective. Furthermore, diffuse clinical patterns, such as lymphangitic carcinomatosis or miliary metastases, represent a biological state in which the permissive microenvironment has been entirely subverted. In these scenarios, the recruitment of immunosuppressive myeloid cells and the widespread remodeling of the extracellular matrix occur throughout the organ, rather than at discrete foci, rendering radical R0 surgical resection anatomically and biologically impossible. Even in cases where the disease remains localized and biologically amenable to resection, the patient's physiological reserve must be considered; for those deemed to have prohibitive surgical risk, nonoperative techniques, such as radiofrequency ablation or stereotactic body radiation therapy, may be preferred to maintain local control.[68]

When comparing these two groups through the lens of tumor biology, the distinction becomes clear: the surgical group comprises tumors that exploit the lung's vascular and mechanical features to establish isolated, often chemoresistant niches that can be surgically removed. Conversely, the non-surgical group encompasses malignancies that either utilize the lung's lymphatic and immune-suppressive frameworks to achieve systemic infiltration or possess a molecular vulnerability that is more effectively addressed via pharmacological disruption. Ultimately, the decision to proceed with metastasectomy is a clinical judgment about whether the disease remains a series of localized biological events or has transitioned into a systemic state that transcends the boundaries of surgical clearance.

Comparative Clinical Perspectives on Surgically Manageable Pulmonary Metastases

A comparative analysis of secondary pulmonary malignancies originating from renal cell carcinoma, germ cell tumors, colorectal carcinoma, and sarcomas further demonstrates how these specific biological characteristics govern the strategic implementation of pulmonary metastasectomy. While all four malignancies disseminate hematogenously and utilize the lung's dense capillary network as a primary site for secondary colonization, their clinical management is governed by distinct histological behaviors and sensitivities to systemic therapy. Sarcomas and RCC represent a category in which surgical intervention is of paramount importance. Due to their relative resistance to conventional chemotherapy, radical resection often serves as the only definitive modality for achieving long-term survival or cure.[69,70] In these cases, the pulmonary microenvironment acts as a critical battleground where the physical elimination of chemoresistant niches is essential. Conversely, GCTs represent a unique biological paradigm characterized by extreme sensitivity to cisplatin-based regimens. In this context, metastasectomy is typically reserved as a post-chemotherapy adjunctive measure to address residual masses, facilitating the differentiation between necrotic tissue, mature teratoma, and viable malignancy.[71]

From a procedural perspective, colorectal carcinoma introduces an additional layer of biological complexity, as it more commonly disseminates via the lymphatic system, in contrast to the predominantly hematogenous spread observed in sarcomas and RCC. This has necessitated a shift in surgical philosophy for CRC, where formal lymphadenectomy or systematic sampling is strongly advocated due to the profound prognostic implications of occult nodal involvement.[72] While the objective of achieving an R0 resection remains the universal gold standard across all groups, the technical approach varies; for instance, the aggressive pursuit of repeat metastasectomies is particularly common in young GCT and sarcoma patients to manage the high rate of recurrence.[71] Ultimately, the transition from primary tumor biology to surgical practice across these four groups reflects a tailored oncological strategy. For GCT, surgery is both a diagnostic and curative completion of systemic treatment. On the other hand, for sarcomas and RCC, it is the primary pillar of local control. For CRC, it is a multidisciplinary step integrated into a broader systemic and potentially multi-organ metastatic framework.[72]

Treatment Goals and Future Direction

Although significant progress has been made in understanding the mechanisms underlying cancer growth and spread, it remains difficult to elucidate the metastasis process due to its complex nature. However, despite the success of immunotherapy in certain primary tumors, no uniformly effective treatment for metastatic disease has yet been established.[73,74]

Therapies targeting early metastatic drivers, including metabolic, angiogenic, and EMT-related pathways, have thus far shown limited clinical efficacy. Greater therapeutic promise may lie in combinatorial approaches, particularly integrating immunotherapy with metabolic inhibition. However, the development of personalized or targeted treatments for metastatic disease remains challenging due to the paucity of actionable mutations and pronounced tumor heterogeneity.[17,75–77] Notably, disseminated tumor cells (DTCs) that colonize the lung may enter dormancy, presenting a potential therapeutic window to reduce recurrence. Although the molecular regulation of dormancy is increasingly understood, accumulating evidence underscores a critical role for the local microenvironment. These observations highlight the multifactorial nature of cancer dormancy and the need to target both tumor-intrinsic and microenvironmental determinants in therapeutic strategies.[78,79]

Conclusion

In conclusion, metastatic cancer remains a complex and challenging process responsible for the majority of cancer-related deaths. While our understanding of the mechanisms underlying metastasis has grown significantly in recent years, effective treatments for metastatic disease remain elusive. The unique characteristics of the pulmonary system, including its extensive blood supply, dense capillary network, and thin membrane structure, make the lungs particularly susceptible to metastatic colonization. The formation of pre-metastatic niches in the lungs, driven by factors released from primary tumors, supports the establishment and growth of disseminated tumor cells.

Future advances in the treatment of metastatic disease will require a comprehensive understanding of these complex, interacting processes. Multi-targeted therapeutic approaches addressing multiple aspects of the metastatic cascade are likely necessary. Some promising areas for further research and therapeutic development include:

- Targeting the formation of pre-metastatic niches.
- Disrupting tumor cell dormancy or preventing reactivation.
- Enhancing anti-tumor immune responses.
- Inhibiting angiogenesis and vascular remodeling.
- Developing combination therapies that address both cancer cell-intrinsic and microenvironmental factors.

Additionally, a better understanding of the molecular and genetic drivers of metastasis may enable personalized treatment approaches for individual patients and tumor types.

While significant challenges remain, ongoing research into the intricacies of the metastatic process continues to uncover new potential therapeutic targets and strategies. Ultimately, improving outcomes for patients with metastatic disease will require continued collaboration between researchers and clinicians to translate mechanistic insights into effective clinical interventions. With further advances in our understanding of pulmonary metastasis, there is hope that more effective treatments can be developed to prevent and combat this lethal aspect of cancer progression.[18,66,67]

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