Mechanisms of Hepatocellular Carcinoma Metastasis: How Liver Cancer Spreads to Distant Sites

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and ranks among the leading causes of cancer-related mortality worldwide. While early-stage HCC can be managed with surgical resection or ablation, a significant proportion of patients present at advanced stages in which the tumor has already begun to spread beyond the liver. This paper examines the key biological mechanisms underlying HCC metastasis, with a particular focus on how tumor cells invade local vasculature, enter systemic circulation, and colonize distant organs. We discuss the roles of epithelial-mesenchymal transition (EMT), microvascular invasion (MVI), and the tumor microenvironment (TME) in enabling this dissemination. We further describe the most common sites of extrahepatic spread — the lungs, regional lymph nodes, bone, and adrenal glands — and the routes by which cancer cells reach each. Understanding these mechanisms is critical for developing more effective staging approaches and targeted therapies for advanced HCC.

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1. Introduction

Liver cancer represents a major global health burden, with projections suggesting new cases could exceed one million annually in the coming years. Hepatocellular carcinoma accounts for approximately 90% of all primary liver cancers and is most commonly associated with chronic hepatitis B or C virus infection, alcohol-related liver disease, and metabolic conditions such as non-alcoholic fatty liver disease (NAFLD). Because HCC typically develops against a background of cirrhosis and often produces no symptoms in its early stages, the majority of patients are diagnosed at advanced or inoperable stages.

The defining feature that most determines prognosis in HCC is metastasis — the spread of tumor cells from the liver to secondary sites in the body. Metastatic disease substantially reduces the available treatment options and sharply worsens survival outcomes. The 5-year survival rate for metastatic hepatic

carcinoma is approximately 14%, reflecting the poor response of disseminated disease to currently available therapies.

HCC spreads both within the liver (intrahepatic metastasis) and beyond it (extrahepatic metastasis). Intrahepatic spread occurs in over 80% of cases involving large primary tumors, typically through invasion of the portal vein system. Extrahepatic spread, while less common at initial diagnosis, occurs frequently as disease progresses and is associated with significantly worse outcomes.

This paper focuses on the mechanisms that drive HCC metastasis: how tumor cells acquire invasive properties, how they breach vascular barriers, how they survive in circulation, and how they establish themselves in distant tissues.

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2. The Metastatic Cascade in HCC

Metastasis is not a single event but a multi-step biological process. For an HCC cell to successfully colonize a distant organ, it must complete a series of sequential steps:

1. **Local invasion**: The tumor cell detaches from the primary tumor mass and invades the surrounding extracellular matrix (ECM).
2. **Intravasation**: The invasive cell penetrates the wall of a blood or lymphatic vessel and enters circulation.
3. **Survival in circulation**: The cell must evade immune surveillance and survive as a circulating tumor cell (CTC).
4. **Extravasation**: The CTC exits the bloodstream at a distant site.
5. **Colonization**: The cell establishes a micrometastasis and adapts to the foreign tissue environment, eventually forming a macrometastasis.

Each of these steps involves distinct molecular mechanisms, and failure at any step terminates the metastatic process. However, HCC cells have developed multiple strategies to complete this cascade successfully.

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3. Epithelial-Mesenchymal Transition (EMT)

One of the most well-characterized drivers of metastatic initiation in HCC is epithelial-mesenchymal transition (EMT). This is a biological process in which epithelial cells — which normally adhere tightly to one another and to the basement membrane — acquire mesenchymal properties characterized by increased motility, invasiveness, and resistance to apoptosis.

In HCC, EMT is triggered by multiple upstream signals, including activation of the Wnt/β-catenin pathway, TGF-β signaling, and the hypoxic microenvironment created by poorly vascularized tumor

regions. During EMT, key epithelial markers such as E-cadherin are downregulated, while mesenchymal markers such as vimentin and N-cadherin are upregulated. The loss of E-cadherin is particularly important: it disrupts cell-cell adhesion and allows tumor cells to detach from the primary mass.

Pathological studies of extrahepatic HCC metastases have confirmed that EMT-high features — including fibrous tumor stroma and high immune cell infiltration — are significantly associated with lymph node metastasis specifically, suggesting that EMT plays a particularly important role in the lymphatic route of spread.

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4. Microvascular Invasion and Portal Vein Involvement

A defining and clinically significant feature of HCC is its strong tendency to invade the hepatic and portal venous systems. Microvascular invasion (MVI) refers to the microscopic presence of tumor cells within small vessels — portal venules, hepatic sinusoids, or capsular vessels — that are only detectable on histological examination. Macrovascular invasion refers to visible tumor thrombus within major vessels such as the main portal vein or hepatic veins.

MVI is one of the strongest independent predictors of extrahepatic metastasis. Studies have identified MVI, alongside vessels encapsulating tumor clusters (VETC), elevated Keratin 19 (K19) expression, and fibroblast-associated protein (FAP) expression as independent factors associated with extrahepatic spread.

Once HCC cells invade the portal vein, they can disseminate throughout the liver via the portal circulation, explaining the high rate of intrahepatic satellite nodules in advanced disease. Cells that reach the hepatic veins can enter the inferior vena cava and then the systemic circulation, with the lungs — the first capillary bed encountered — becoming the most frequent site of distant metastasis.

In advanced cases, tumor thrombus can extend from the hepatic veins through the inferior vena cava and into the right atrium, a finding that carries a particularly poor prognosis and eliminates candidacy for surgical resection.

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5. The Tumor Microenvironment and Immune Evasion

The tumor microenvironment (TME) in HCC is a complex ecosystem composed of cancer cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), endothelial cells, and various immune cell populations. This environment actively facilitates metastatic behavior.

Tumor-associated macrophages, particularly those polarized to the M2 phenotype, play a prominent role in promoting HCC invasion and dissemination. M2 TAMs secrete vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), which promote angiogenesis — the formation of new blood vessels that the tumor exploits for both nourishment and intravasation. They also secrete matrix

metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and create physical pathways for tumor cell migration. Additionally, M2 TAMs contribute to immune evasion by producing IL-10, TGF-β, and PGE2, suppressing anti-tumor T cell activity and allowing tumor cells to persist and spread undetected.

Elevated CD163+ macrophage infiltration has been identified as an independent factor predicting extrahepatic metastasis, further underscoring the central role of TAMs in enabling HCC spread.

The hypoxic core of rapidly growing HCC tumors drives additional pro-metastatic changes. Hypoxia-inducible factors (HIFs) upregulate genes involved in angiogenesis, glycolytic metabolism, and EMT, creating a self-reinforcing cycle that accelerates invasion.

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6. Hematogenous vs. Lymphatic Dissemination

HCC spreads through two principal systemic routes: hematogenous (via the bloodstream) and lymphatic (via lymph vessels). These routes are associated with distinct metastatic patterns.

Hematogenous spread is the primary route for distant metastases to the lungs, bone, adrenal glands, and brain. Tumor cells enter the hepatic or portal veins and are carried to the systemic circulation. Because the lungs receive all venous return from the body, they are the first major capillary filter encountered, explaining why pulmonary metastases are the most common extrahepatic manifestation, occurring in approximately 55% of patients with extrahepatic HCC.

Lymphatic spread predominantly results in regional lymph node involvement. In one study of 403 patients with HCC, 41% had regional lymph node metastasis, with the periceliac nodes most commonly involved (33%), followed by the portohepatic nodes (23%). Distant nodal metastases most commonly occur in the mediastinum. Pathologically, lymph node metastases in HCC are associated with EMT-high tumor phenotypes and K19 expression, in contrast to the VETC and macrotrabecular-massive (MTM) subtypes more commonly associated with pulmonary metastases.

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7. Common Sites of Extrahepatic Metastasis

7.1 Lungs

The lung is the most common site of extrahepatic HCC metastasis, affected in approximately 55% of patients with documented extrahepatic disease. Pulmonary metastases typically appear as multiple bilateral nodules and arise via hematogenous spread through the hepatic veins into the systemic circulation. They are often small and peripherally located, frequently detected on CT imaging before the patient becomes symptomatic.

7.2 Lymph Nodes

Regional lymph nodes represent the second most common site of extrahepatic spread. Involvement of the periceliac, portohepatic, and mediastinal nodal chains is most frequently observed. Lymphadenopathy in the setting of HCC must be distinguished from reactive lymph node enlargement commonly seen in patients with underlying hepatitis or cirrhosis; features such as central necrosis and peripheral enhancement on contrast-enhanced CT raise concern for malignant involvement.

7.3 Bone

Skeletal metastases occur in approximately 28% of patients with extrahepatic HCC. They are typically lytic and hypervascular in nature and most commonly affect the lumbosacral spine, thoracic vertebrae, ribs, and long bones. Bone metastases frequently present with skeletal pain or pathologic fractures, and occasionally represent the initial clinical presentation of HCC before a hepatic primary is identified. Multiple bony lesions are common.

7.4 Adrenal Glands

The adrenal glands are a less common but recognized site of HCC metastasis. Adrenal involvement typically occurs via hematogenous spread and may be bilateral. On imaging, adrenal HCC metastases may be difficult to distinguish from adrenal adenomas, requiring careful attention to vascularity, signal characteristics on MRI, and correlation with the clinical context.

7.5 Other Sites

Less common sites of extrahepatic spread include the brain, diaphragm, peritoneum, and gastrointestinal tract. Rare cases of metastasis to the sternum, ovaries, and pharyngeal lymph nodes have been reported in the literature. Brain metastases from HCC are uncommon but carry a particularly poor prognosis, given limited therapeutic options and the fragile hepatic function of most affected patients.

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8. Genetic and Molecular Drivers

The metastatic potential of HCC is substantially shaped by its genetic landscape. Three tumor suppressor genes — TP53, RB1, and PTEN — are among the most significantly recurrent mutations in extrahepatic metastases. Loss of TP53 function disrupts apoptotic checkpoints and allows genomically unstable cells to survive and proliferate. RB1 and PTEN loss further relieve restraints on cell cycle progression and PI3K/Akt signaling, respectively.

Studies using single-cell RNA sequencing have identified two hepatocyte subpopulations with distinct metastatic tendencies: lymph node metastasis-associated hepatocytes (LNNMAHs) and portal vein metastasis-associated hepatocytes (PVMAHs), suggesting that the specific route of metastatic spread is partially encoded at the cellular level within the primary tumor.

Aberrant activation of the Wnt/β-catenin pathway — present in 20–35% of HCC cases — is associated with EMT and contributes to the stem-like properties of metastasis-initiating cells. The insulin-like growth factor (IGF) signaling pathway similarly promotes invasion and metastatic progression.

Epigenetic alterations, including aberrant DNA methylation and histone modification, further modulate the expression of pro-metastatic genes without altering the underlying DNA sequence. Three-dimensional genome structural remodeling — changes in how chromatin is organized within the nucleus — has emerged as an additional layer of regulation, influencing the accessibility of metastasis-associated gene loci.

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9. Clinical Implications

The mechanisms described above have direct implications for the clinical management of HCC.

Staging: Accurate identification of extrahepatic metastases is essential for staging and treatment planning. The presence of extrahepatic disease eliminates candidacy for surgical resection and liver transplantation, directing patients instead toward systemic therapy. Contrast-enhanced CT of the chest, abdomen, and pelvis, supplemented by bone scintigraphy where indicated, forms the basis of standard metastatic workup.

Biomarkers: Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomal contents hold promise as minimally invasive biomarkers for detecting early metastatic dissemination before imaging findings become apparent.

Systemic therapy: Sorafenib, a multi-kinase inhibitor targeting VEGFR and other pro-angiogenic pathways, remains a cornerstone first-line systemic agent for advanced HCC with extrahepatic spread. Lenvatinib and regorafenib represent additional approved options in the first- and second-line settings, respectively. Immunotherapy combinations, particularly atezolizumab plus bevacizumab, have demonstrated improved survival over sorafenib in selected populations and are increasingly used as first-line treatment.

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10. Conclusion

HCC metastasis is a complex, multi-step process driven by the interplay of genetic mutations, epigenetic reprogramming, EMT, vascular invasion, and a permissive tumor microenvironment. The liver's dual blood supply and the tumor's inherent tendency to invade the portal and hepatic venous systems provide efficient highways for both intrahepatic and systemic spread. The lungs, lymph nodes, bone, and adrenal glands are the most clinically important sites of extrahepatic colonization, each reached through distinct anatomical routes.

Advances in single-cell sequencing, liquid biopsy, and molecular profiling are steadily improving our understanding of the cellular and molecular heterogeneity underlying HCC metastasis. Translating these insights into earlier detection strategies and more effective targeted therapies remains one of the central challenges in hepatic oncology.

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