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Epithelial–Mesenchymal Transition in Cancer Progression: Biological Basis and Histopathological Implications

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Abstract

Background: Epithelial–mesenchymal transition (EMT) is a fundamental biologic process that plays a critical role in tumor invasion, metastasis, and dedifferentiation. While extensively investigated in molecular oncology, its relevance to routine surgical pathology practice remains underemphasized. Many morphologic alterations observed in daily histopathologic evaluation represent phenotypic manifestations of EMT, yet these findings are often interpreted descriptively without integration into a unified biologic framework.
Methods: This review aims to provide a practical overview of EMT from a surgical pathology perspective by correlating biologic mechanisms with histomorphologic features, immunohistochemical findings, and clinical implications across solid tumors.A narrative literature review was conducted using PubMed/MEDLINE databases to identify relevant studies published between 2020 and 2025. Keywords related to EMT, histopathology, tumor progression, and immunohistochemistry were applied. Selected articles were qualitatively synthesized with emphasis on clinicopathologic relevance and applicability to routine diagnostic practice.
Results: EMT is characterized by loss of epithelial differentiation, acquisition of mesenchymal traits, and increased cellular plasticity. Histologically, EMT correlates with recognizable features including loss of cellular cohesion, tumor budding, single-cell invasion, spindle cell transformation, and tumor dedifferentiation. Immunohistochemical alterations such as decreased E-cadherin expression and increased mesenchymal marker expression further support EMT-associated phenotypes. Across multiple organ systems, these morphologic changes are consistently associated with aggressive tumor behavior, metastatic potential, and therapeutic resistance.
Conclusion: Epithelial–mesenchymal transition (EMT) is a key biological process driving tumor invasion, metastasis, and dedifferentiation in epithelial malignancies. Beyond molecular alterations, EMT shows recognizable histopathologic features such as loss of cohesion, tumor budding, spindle cell change, and infiltrative growth, reflecting increased cellular plasticity. Occurring along a dynamic continuum, EMT explains intratumoral heterogeneity and correlates with aggressive behavior, therapy resistance, and poor prognosis. Recognition of EMT-related morphology provides a practical bridge between traditional histopathology and modern cancer biology, supporting prognostic assessment and reinforcing the ongoing relevance of morphologic evaluation in precision oncology.

Keywords: *epithelial–mesenchymal transition, histopathology, dedifferentiation, immunohistochemistry, cancer progression.*

Introduction

Cancer progression is a dynamic biological process characterized by the acquisition of invasive and metastatic capabilities. One of the most important mechanisms underlying this transformation is epithelial–mesenchymal transition (EMT), a biologic program in which epithelial cells lose their polarity and intercellular adhesion while acquiring mesenchymal features, enhanced motility, and invasive potential. Initially described in embryogenesis and wound healing, EMT has increasingly been recognized as a central process in tumor progression and metastasis across a wide spectrum of human malignancies.[1]

In surgical pathology practice, many morphologic changes routinely observed under the microscope reflect biological processes consistent with EMT. Features such as loss of cellular cohesion, tumor budding, single-cell infiltration, spindle cell morphology, and sarcomatoid transformation are frequently encountered in aggressive tumors. However, these histologic findings are often interpreted descriptively without integration into a unifying biological framework. Understanding EMT provides a conceptual bridge linking traditional morphologic assessment with modern cancer biology.[2]

Recent advances in molecular oncology have demonstrated that EMT is regulated by complex signaling pathways, including transforming growth factor-β (TGF-β), Wnt/β-catenin, and multiple transcription factors such as SNAIL, SLUG, TWIST, and ZEB families. These molecular alterations ultimately result in characteristic phenotypic shifts, including downregulation of epithelial markers (e.g., E-cadherin) and upregulation of mesenchymal markers (e.g., vimentin and N-cadherin). Importantly, these molecular events often correlate with recognizable histopathologic patterns, suggesting that routine microscopic evaluation remains highly relevant in identifying EMT-associated tumor behavior.[1,3-6]

Despite extensive molecular research, the practical implications of EMT for diagnostic pathologists remain underemphasized. Most reviews focus predominantly on signaling mechanisms rather than on morphologic correlates observable in daily histopathology practice. Consequently, there is a need for a practical synthesis that highlights how EMT manifests across different tumor types and how pathologists can recognize its histologic footprints using routine hematoxylin–eosin examination and commonly available immunohistochemical markers.

This review aims to provide a practical overview of epithelial–mesenchymal transition from a surgical pathology perspective, emphasizing histomorphologic features, immunohistochemical correlates, and clinical implications across solid tumors. By integrating molecular concepts with routine diagnostic observations, this article seeks to enhance the understanding of EMT as a biologically meaningful process directly relevant to everyday pathology practice.

Methods

The primary objective of this review is to present epithelial–mesenchymal transition (EMT) from a practical surgical pathology perspective, emphasizing its relevance to routine histopathologic evaluation. This article aims to bridge the gap between rapidly expanding molecular knowledge and the morphologic features commonly encountered by pathologists in daily diagnostic practice.

Specifically, this review seeks to: (1) summarize the fundamental biological concepts underlying EMT in cancer progression; (2) describe the key histomorphologic features that may represent morphologic correlates of EMT across solid tumors; (3) discuss immunohistochemical markers that can support the recognition of EMT-associated phenotypes using widely available diagnostic tools; and (4) highlight the clinical implications of EMT, including its association with tumor aggressiveness, metastatic potential, and therapeutic resistance.

The scope of this review focuses on solid epithelial malignancies frequently encountered in general surgical pathology practice. The discussion emphasizes practical interpretation and pattern recognition that may assist pathologists in integrating EMT-related concepts into routine diagnostic reporting and clinicopathologic correlation.

Study Design

This study was conducted as a narrative literature review aimed at summarizing the biological basis, histomorphologic manifestations, immunohistochemical correlates, and clinical implications of epithelial–mesenchymal transition (EMT) from a surgical pathology perspective. The review focused on integrating molecular concepts with practical histopathologic findings relevant to routine diagnostic practice.

Literature Search Strategy

A structured literature search was performed using electronic databases including PubMed/MEDLINE. Articles published in English between January 2020 and December 2024 were considered to capture both foundational and recent developments related to EMT in human malignancies.

The search strategy included combinations of the following keywords: “epithelial–mesenchymal transition,” “EMT,” “histopathology,” “tumor budding,” “dedifferentiation,” “sarcomatoid carcinoma,” “immunohistochemistry,” “E-cadherin,” “vimentin,” and “cancer progression.” Additional organ-specific searches were performed using terms such as “colorectal carcinoma,” “breast carcinoma,” “lung carcinoma,” and “thyroid carcinoma” combined with “EMT.” Reference lists of relevant articles were manually reviewed to identify additional eligible studies.

Eligibility Criteria

Articles were included if the arcticle discussed EMT in human epithelial malignancies, provided histopathologic, immunohistochemical, or clinicopathologic correlations, and were original research articles, review articles, or consensus guidelines relevant to surgical pathology practice.

Data Extraction and Synthesis

Relevant information regarding morphologic features, immunohistochemical findings, and clinical implications associated with EMT was extracted and qualitatively synthesized. Emphasis was placed on findings applicable to routine hematoxylin–eosin evaluation and commonly available immunohistochemical markers. Rather than performing quantitative meta-analysis, the collected evidence was integrated into a practical, organ-based interpretative framework intended for diagnostic pathologists.

Results

Biological Basis of Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT) is a biologic process in which epithelial cells undergo phenotypic reprogramming characterized by loss of epithelial differentiation and acquisition of mesenchymal properties. During this transition, cells lose apical–basal polarity and intercellular adhesion while gaining migratory capacity, invasiveness, and resistance to apoptosis. Although EMT has been extensively studied in developmental biology, it is now recognized as a key mechanism contributing to tumor progression and metastatic dissemination (figure 1).[4]

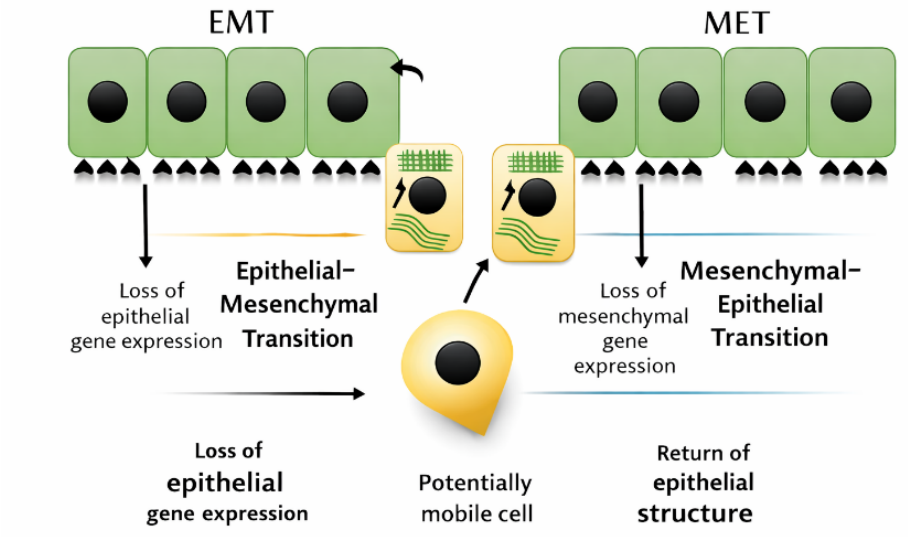

Figure 1. Basic mechanism of EMT. Epithelial cell loose their marker and become cell with mesenchymal marker to promote progression and metastasis

Types of EMT

Based on biologic context and functional outcomes, EMT has been broadly classified into three distinct types (figure 2)[6]:

Type 1 EMT (Developmental EMT) occurs during embryogenesis and organ development, where epithelial cells transition into migratory mesenchymal cells, facilitating the generation of diverse tissues and structures. This process is tightly regulated and does not lead to fibrosis or malignant transformation. In contrast, Type 2 EMT (Repair-Associated EMT) is observed in tissue repair, regeneration, and chronic inflammation. It plays a critical role in wound healing by enabling epithelial cells to migrate and restore tissue integrity. However, persistent activation of Type 2 EMT may contribute to fibrotic diseases through excessive extracellular matrix deposition. Lastly, Type 3 EMT (Oncogenic EMT) is associated with carcinoma progression and is the form most relevant to surgical pathology. In malignant tumors, EMT promotes local invasion, intravasation, metastatic spread, and therapeutic resistance. Unlike developmental EMT, oncogenic EMT is often incomplete or reversible, leading to hybrid epithelial–mesenchymal phenotypes that retain partial epithelial characteristics while acquiring invasive behavior.

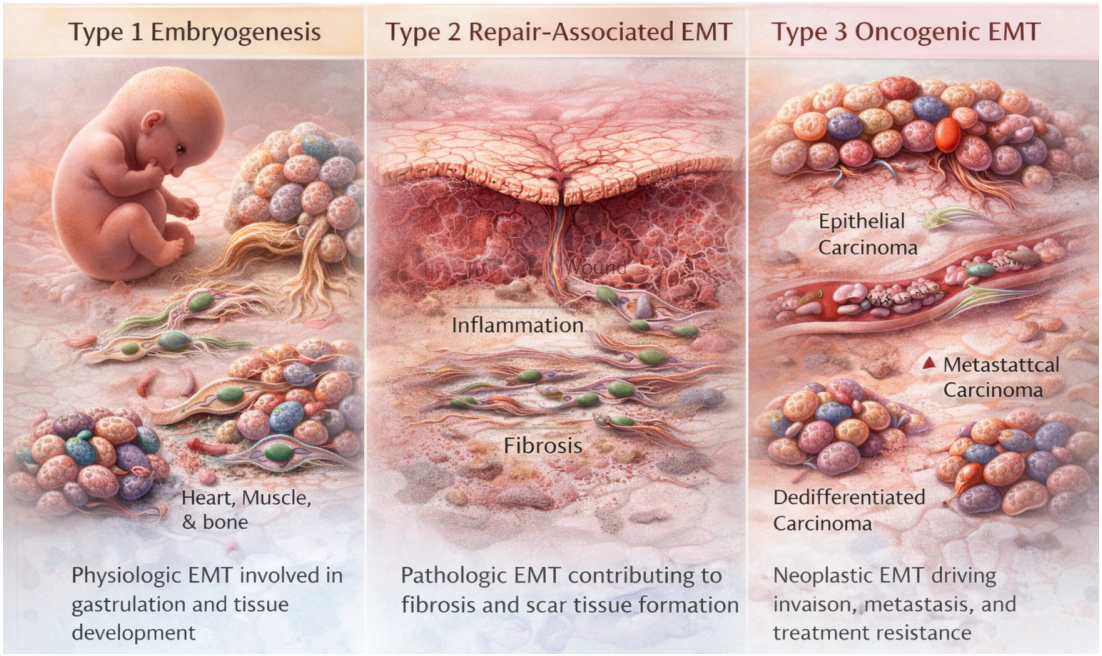

Figure 2. EMT types. Type 1: Embryogenesis (Physiologic EMT). This type occurs during the earliest stages of life. It is a normal, healthy part of development. It is involved in gastrulation (when an embryo develops its layers) and the formation of specific organs. The result is these cells differentiate into structural components like Heart, Muscle, & Bone. Type 2: Repair-Associated EMT (Pathologic EMT). This type is triggered as a response to injury or chronic stress. It begins with a wound and Inflammation. The epithelial cells transform into mesenchymal cells (fibroblasts) to reconstruct the area. The result is production of Fibrosis and scar tissue. But If the process doesn't stop, it leads to organ scarring (like liver or kidney fibrosis), which can impair organ function. Type 3: Oncogenic EMT. It drives the progression of an Epithelial Carcinoma (a localized tumor), loose their specific identity and gain the ability to move. They break away from the primary tumor and enter the bloodstream or lymph system. This leads to Invasion and Metastasis and contributes to Treatment Resistance

At the cellular level, EMT is characterized by functional and structural changes that include dissolution of adherens junctions, cytoskeletal reorganization, and alterations in cell–matrix interactions. A hallmark molecular event is the downregulation of epithelial markers, particularly E-cadherin, accompanied by increased expression of mesenchymal markers such as vimentin and N-cadherin. These phenotypic alterations are orchestrated by several transcription factors, including SNAIL, SLUG, TWIST, and ZEB families, which regulate gene expression programs associated with cellular plasticity.[7]

Partial EMT and Cellular Plasticity in Cancer

Increasing evidence suggests that EMT in cancer rarely occurs as a complete transition. Instead, tumor cells frequently exhibit intermediate or “partial EMT” states, demonstrating both epithelial and mesenchymal features simultaneously. This cellular plasticity explains why many tumors maintain epithelial morphology while displaying aggressive infiltrative patterns histologically. The concept of partial EMT is particularly important for pathologists, as subtle morphologic alterations—such as tumor budding or single-cell invasion—may represent early manifestations of this transitional state (figure 3). [8-10]

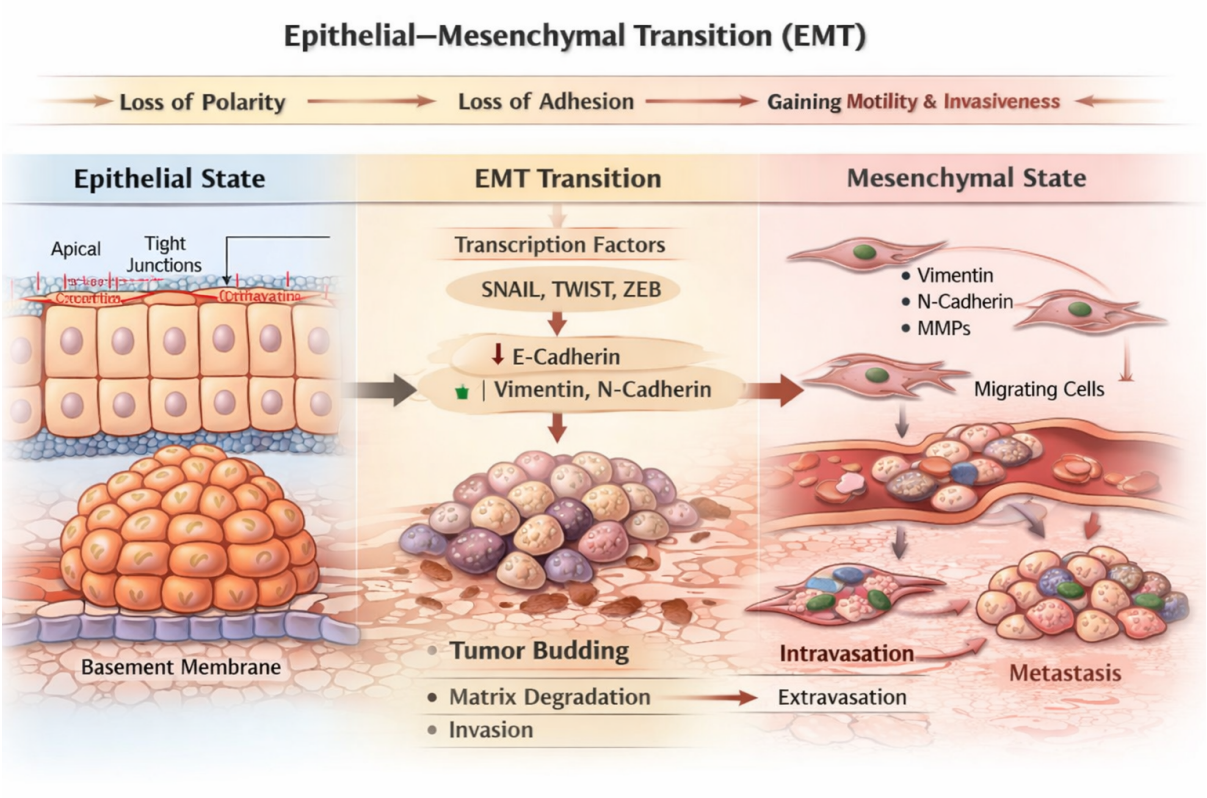

Figure 3. EMT process in cancer. Normal epithelial cells are characterized by Apical-Basal Polarity and are held tightly together by Tight Junctions. They are securely attached to the Basement Membrane, which acts as a physical barrier preventing cells from wandering into other tissues. The transtition process is triggered by specific "master switch" proteins, notably SNAIL, TWIST, and ZEB. These proteins instruct the cell to change its identity. A hallmark of EMT is the downregulation of E-Cadherin (the "glue" that keeps cells together) and the upregulation of N-Cadherin and Vimentin, which provide the cell with the flexibility to move. As cells lose their adhesion, they begin to break away from the primary tumor mass, a phenomenon known as "budding." The cells gain a spindle-like shape and produce enzymes called MMPs (Matrix Metalloproteinases) that degrade the surrounding tissue. These newly mobile cells physically push through tissue to enter the blood vessels. Once they travel through the bloodstream, they exit the vessel at a distant site (Extravasation) to form a new tumor, completing the process of metastasis.

Histomorphologic Manifestations of EMT in Surgical Pathology

Epithelial–mesenchymal transition (EMT) is a biological process that enables carcinoma cells to acquire the ability to invade, migrate, and disseminate metastatically. From a surgical pathology perspective, EMT is not just a molecular phenomenon but is marked by distinct morphological alterations that indicate increasing tumor aggressiveness. One of the earliest signs of EMT is the loss of cellular cohesion and architectural disruption. In normal epithelial tumors, cohesive growth is maintained by adhesion molecules like E-cadherin, but during EMT, reduced cell-cell adhesion leads to fragmentation of tumor nests and irregular invasive borders. This manifests histologically as poorly cohesive tumor clusters or scattered individual cells infiltrating surrounding tissues,

reflecting a shift toward a motile and invasive phenotype. Tumor budding, characterized by isolated cells or small clusters of tumor cells at the invasive front, is another key morphologic feature of EMT. These budding cells exhibit reduced differentiation, increased nuclear atypia, and enhanced stromal interaction, allowing for increased migratory capability and playing a crucial role in local invasion and early metastatic spread. Tumor budding has been linked to poor prognosis in various carcinomas, underscoring its significance as an EMT-related phenomenon. As EMT progresses, carcinoma cells may undergo cytoskeletal reorganization, leading to an elongated or spindle-shaped morphology. This transformation marks the acquisition of mesenchymal characteristics that aid in motility through the extracellular matrix. In more extreme cases, tumors may demonstrate sarcomatoid or spindle cell differentiation, losing conventional epithelial architecture. These changes represent advanced stages of EMT and are often associated with aggressive clinical behavior and resistance to therapy. EMT also enhances stromal interactions, where tumor cells remodel the extracellular matrix and recruit fibroblasts and inflammatory cells, often resulting in desmoplasia and irregular infiltrative growth. This dynamic interface between the tumor and stroma facilitates invasion, allowing tumor cells to penetrate vascular and lymphatic channels. Finally, EMT leads to dedifferentiation and the loss of lineage identity. As epithelial differentiation is suppressed, tumor cells lose organ-specific features and adopt poorly differentiated or anaplastic appearances. This dedifferentiation reflects increased cellular plasticity, enabling tumor cells to adapt to environmental stress, evade immune surveillance, and survive during metastatic dissemination.[6,10]

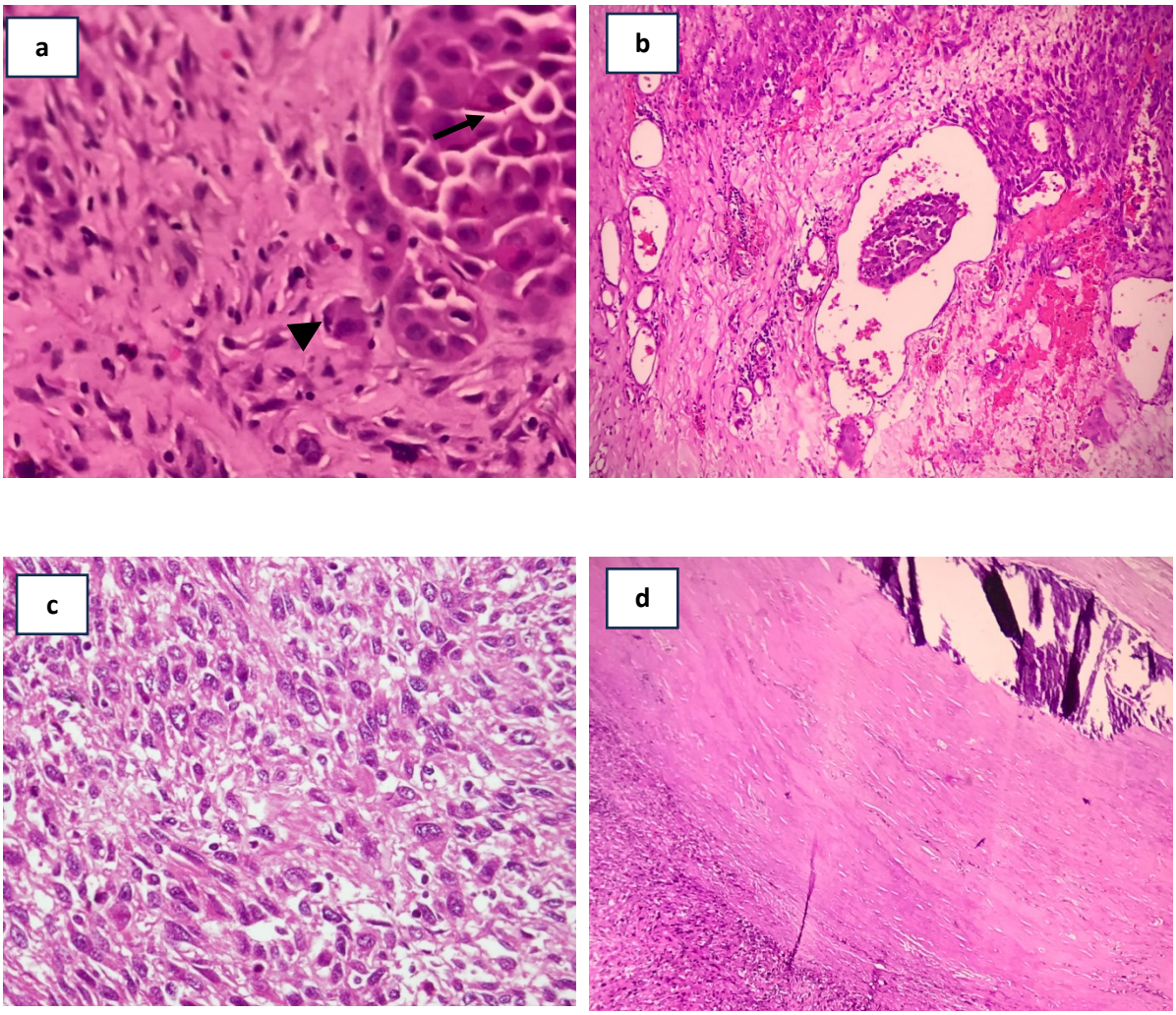

Figure 3. EMT in histopathology. A. Loose of cellular cohesion (arrow) and tumor budding (head arrow). B. Lymphovascular invasion as a result of tumor budding and single cell invasion. C. Spindle cell transformation (sarcomatoid differentiation). D. Stromal desmoplasia

EMT Across Organ Systems: Practical Histopathologic Perspectives

Although epithelial–mesenchymal transition (EMT) represents a shared biologic mechanism in carcinoma progression, its morphologic expression varies across organ systems. Recognition of EMT-associated patterns in different tumors allows pathologists to interpret aggressive behavior through routinely observed histologic features. Across organs, EMT commonly manifests as loss of cohesion, infiltrative growth, tumor budding, spindle cell transformation, and dedifferentiation, reflecting increasing cellular plasticity and metastatic capability (table 1).

Table 1. Prognostic Significance of Epithelial–Mesenchymal Transition (EMT) Markers Across Major Human Cancers

Cancer Type	Key EMT Markers Reported	Biological EMT Features	Typical Histopathologic Finding	Prognostic Implication	Pathological Correlation
Breast carcinoma[17-20]	Loss of E-cadherin, increased N-cadherin, Vimentin, Snail, Twist	Cadherin switching and cytoskeletal remodeling	Invasive front heterogeneity, metaplastic differentiation, tumor budding	Associated with high grade tumors, metastasis, chemoresistance and poor overall survival	Common in triple-negative and basal-like subtype
Non-small cell lung carcinoma (NSCLC)[21-24]	Reduced E-cadherin, increased Vimentin, ZEB1, TWIST1	Partial EMT phenotype	Micropapillary/solid pattern, stromal invasion	Therapy resistance (especially EGFR-TKI) and disease progression	Frequently observed in invasive tumor areas, poor differentiation and early dissemination
Thyroid carcinoma (PDTC & ATC)[25-28]	Loss of E-cadherin, increased Vimentin, Snail, TGF-β signaling activation	Dedifferentiation and increased cellular motility	Transition from PTC → PDTC → anaplastic morphology, spindle/giant cells	Strong association with aggressive behavior and mortality, and radioiodine resistance	Correlates with loss of follicular differentiation
Colorectal carcinoma[29-31]	Nuclear β-catenin, ZEB1, Snail, decreased E-cadherin	Wnt/β-catenin–driven EMT activation	Single cells or small clusters at invasive front	Lymph node metastasis, tumor budding, reduced survival	Prominent at invasive tumor front
Head and neck squamous cell carcinoma[32-34]	Reduced E-cadherin, increased Vimentin, TWIST, ZEB2	EMT activation at invasion margins	Discohesive cells, stromal desmoplasia	Increased recurrence, nodal metastasis and poor disease-free survival	Linked to tumor budding and stromal invasion

Cancer Type	Key EMT Markers Reported	Biological EMT Features	Typical Histopathologic Finding	Prognostic Implication	Pathological Correlation
Pancreatic ductal adenocarcinoma[35-37]	Snail, Slug, ZEB1, TGF-β pathway activation	Early EMT induction and stromal interaction	Prominent desmoplasia, scattered infiltrating glands	Early metastasis and chemoresistance	Associated with desmoplastic stroma
Gastric carcinoma[38,39]	E-cadherin loss (CDH1 alteration), increased Vimentin	Diffuse infiltrative EMT phenotype	Signet-ring or poorly cohesive carcinoma	Poor prognosis, diffuse spread and advanced stage disease	Typical in diffuse/signet-ring subtype
Hepatocellular carcinoma[40,41]	Twist, Snail, TGF-β signaling	EMT-mediated invasion and stemness	Loss of hepatic architecture, infiltrative margins	Microvascular invasion and early recurrence	Associated with aggressive tumor phenotype

Breast Carcinoma

In breast carcinoma, epithelial–mesenchymal transition (EMT) plays a central role in tumor invasiveness and biological aggressiveness, particularly in triple-negative and metaplastic subtypes. Histopathologically, EMT is reflected by loss of cell cohesion, emergence of spindle-shaped tumor cells, and increased heterogeneity at the invasive tumor front. These changes are frequently accompanied by reduced E-cadherin expression and increased mesenchymal markers such as vimentin, SNAIL, and TWIST. EMT contributes to enhanced migratory capacity, resistance to apoptosis, and therapeutic resistance, thereby correlating with higher rates of recurrence and distant metastasis.[19,20]

Non small cell lung Adenocarcinoma

In lung adenocarcinoma, EMT is closely associated with progression from non-invasive or lepidic growth patterns toward invasive phenotypes. Morphologically, tumors demonstrating EMT often exhibit micropapillary, solid, or poorly differentiated components with loss of glandular architecture. Molecularly, activation of transcription factors such as ZEB1 and TWIST leads to downregulation of epithelial adhesion molecules and acquisition of mesenchymal characteristics. These alterations promote tumor dissemination and are strongly associated with poor prognosis, early metastasis, and resistance to targeted therapies. [21,23]

Thyroid Carcinoma

EMT represents a key biological mechanism underlying dedifferentiation in thyroid carcinoma, particularly along the progression spectrum from papillary thyroid carcinoma to poorly differentiated and anaplastic thyroid carcinoma. Histologically, EMT manifests as loss of classical papillary architecture, increased cellular pleomorphism, spindle or giant cell morphology, and infiltrative growth patterns. Molecular alterations include reduced E-cadherin expression and activation of TGF-β signaling pathways with increased mesenchymal marker expression. EMT-driven dedifferentiation contributes to aggressive clinical behavior, loss of radioiodine avidity, and poor clinical outcomes.[25,26,28]

Colorectal Carcinoma

In colorectal carcinoma, EMT is most prominently observed as tumor budding at the invasive front, which is widely recognized as a morphologic surrogate of EMT. Tumor budding consists of single cells or small clusters detached from the main tumor mass, reflecting reduced cell adhesion and increased migratory capability.

Nuclear β-catenin accumulation and activation of EMT-related transcription factors such as ZEB1 support this transition. Numerous studies demonstrate that tumor budding is an independent predictor of lymph node metastasis, local recurrence, and adverse survival outcomes.[29,31]

Head and Neck Squamous Cell Carcinoma

EMT significantly contributes to invasion and regional metastasis in head and neck squamous cell carcinoma (HNSCC). Histopathologically, EMT is characterized by discohesive tumor cells, irregular invasive borders, and prominent stromal interaction accompanied by desmoplasia. Reduced membranous E-cadherin expression together with increased TWIST and SNAIL activity facilitates epithelial plasticity and enhanced motility. These EMT-associated features correlate strongly with lymph node metastasis, treatment resistance, and increased risk of tumor recurrence.[32,33,42]

Gastric Carcinoma

In gastric carcinoma, EMT is particularly relevant in diffuse-type tumors, where loss of epithelial adhesion leads to poorly cohesive or signet-ring cell morphology. Alterations in E-cadherin expression, frequently related to CDH1 dysfunction, promote cellular dissociation and diffuse infiltration of the gastric wall. EMT-associated signaling enhances invasive capacity and contributes to peritoneal dissemination. Clinically, EMT activation is associated with advanced-stage disease and unfavorable prognosis.[38,39]

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma demonstrates early activation of EMT, which contributes to its highly aggressive clinical course. Histologically, EMT is reflected by infiltrative glands embedded within dense desmoplastic stroma and scattered tumor cells showing reduced epithelial differentiation. TGF-β signaling and ZEB1 activation play major roles in promoting mesenchymal phenotypes and immune evasion. EMT facilitates early systemic dissemination, explaining why metastatic disease frequently occurs even in relatively small primary tumors.[35-37]

Hepatocellular Carcinoma

In hepatocellular carcinoma, EMT contributes to tumor invasiveness, vascular infiltration, and recurrence after treatment. Histologically, EMT is suggested by disruption of trabecular architecture, infiltrative margins, and increased cellular atypia. Activation of TGF-β signaling pathways promotes expression of mesenchymal markers including vimentin while reducing epithelial characteristics. EMT-driven changes are strongly associated with microvascular invasion and represent an important predictor of early tumor recurrence.[40,41]

Discussion

Importantly, EMT should not be viewed as an all-or-none event. Many tumors exhibit partial EMT, in which epithelial and mesenchymal features coexist. This explains why tumors may retain epithelial marker expression while simultaneously demonstrating aggressive infiltrative morphology. Recognition of EMT as a continuum helps pathologists interpret subtle histologic findings as biologically meaningful indicators of tumor progression rather than isolated morphologic variations.[34,43]

Multiple signaling pathways contribute to EMT induction, including transforming growth factor-β (TGF-β), Wnt/β-catenin, Notch, and receptor tyrosine kinase signaling. These pathways interact with the tumor microenvironment, inflammatory mediators, and stromal components, collectively promoting phenotypic switching. While these molecular mechanisms are complex, their downstream effects often converge into recognizable morphologic patterns observable in routine histologic examination.[19,44]

Immunohistochemistry (IHC) provides a practical method for identifying phenotypic alterations associated with epithelial–mesenchymal transition (EMT) in routine diagnostic practice. Although EMT is fundamentally a dynamic molecular process, its downstream effects frequently manifest as reproducible changes in protein expression that can be evaluated using widely available antibodies. Recognition of these immunophenotypic shifts allows pathologists to correlate morphologic findings with underlying tumor biology.

A central feature of EMT is the reduction or loss of epithelial differentiation markers, particularly those involved in cell–cell adhesion. Among these, E-cadherin plays a pivotal role in maintaining epithelial cohesion through adherens junctions. Decreased membranous E-cadherin expression is one of the most consistent immunohistochemical indicators of EMT and correlates with loss of cellular cohesion and increased invasiveness.[45] In parallel, alterations in β-catenin localization may occur. While membranous staining is typical of epithelial differentiation, cytoplasmic or nuclear accumulation reflects activation of signaling pathways associated with EMT and tumor progression. These changes may accompany infiltrative growth patterns and tumor budding.[44]

As epithelial characteristics diminish, tumor cells frequently acquire mesenchymal phenotypes detectable by IHC. Vimentin expression represents the most widely used marker of mesenchymal differentiation and is commonly observed in tumors demonstrating spindle morphology or sarcomatoid transformation. Increased vimentin expression reflects cytoskeletal reorganization that enhances cellular motility.[14] Another important phenomenon is the so-called “cadherin switch,” characterized by reduced E-cadherin expression accompanied by increased N-cadherin expression. This shift promotes weaker intercellular adhesion while facilitating interaction with stromal components, thereby enhancing invasive potential.[11]

Although not a direct EMT marker, increased proliferative activity often accompanies EMT-associated tumor progression. Elevated Ki-67 labeling index is frequently observed in tumors showing dedifferentiation or sarcomatoid features, reflecting biologic aggressiveness and rapid tumor evolution. In this context, Ki-67 serves as a supportive indicator of high-grade transformation rather than a specific EMT marker.

Epithelial–mesenchymal transition (EMT) is primarily driven by a group of transcription factors known as EMT-inducing transcription factors (EMT-TFs), which orchestrate the reprogramming of epithelial cells into a mesenchymal phenotype. Key EMT-TFs include the SNAIL family (SNAIL1 and SNAIL2/SLUG), TWIST1/2, and ZEB1/2, which act mainly by repressing epithelial genes such as E-cadherin (CDH1) while activating mesenchymal markers including N-cadherin, vimentin, and fibronectin. These transcription factors are activated downstream of multiple signaling pathways frequently altered in cancer, including TGF-β, Wnt/β-catenin, Notch, Hedgehog, and hypoxia-related signaling. Through epigenetic modification, chromatin remodeling, and interaction with microRNAs, EMT-TFs promote loss of cell–cell adhesion, cytoskeletal reorganization, enhanced motility, and resistance to apoptosis, thereby facilitating tumor invasion, metastasis, and cellular plasticity. Importantly, EMT induction is often reversible, allowing tumor cells to undergo mesenchymal–epithelial transition (MET) at metastatic sites, highlighting the dynamic role of EMT-TFs in cancer progression.[19,26,42]

Tumors undergoing EMT may demonstrate partial loss of lineage-specific markers, reflecting dedifferentiation. For example, reduced expression of organ-specific transcription factors may occur in advanced tumors while residual focal positivity persists. This phenomenon illustrates cellular plasticity, where tumor cells retain minimal epithelial identity while acquiring mesenchymal behavior. Recognition of this pattern is particularly important to avoid diagnostic pitfalls when evaluating poorly differentiated malignancies.[28,46]

It is important to emphasize that no single immunohistochemical marker definitively establishes EMT. Instead, EMT should be interpreted as a composite phenotype integrating morphologic features with coordinated immunophenotypic changes. Evaluation in hotspot invasive areas, tumor budding regions, or dedifferentiated components often provides the most informative assessment. Correlation with histologic architecture remains essential, as immunohistochemistry serves primarily as supportive evidence of biologic transition rather than a standalone diagnostic criterion.[18,38,47]

The transition toward anaplastic morphology reflects profound cellular reprogramming and acquisition of mesenchymal characteristics, enabling rapid local invasion and distant dissemination. In this context, EMT contributes not only to metastatic potential but also to therapeutic resistance and immune evasion. Recognition of early dedifferentiation areas within otherwise differentiated tumors may therefore carry important prognostic implications.

Across organ systems, EMT should be viewed as a morphologic continuum rather than a discrete event. Tumors rarely undergo complete transformation; instead, they demonstrate heterogeneous areas reflecting varying degrees of epithelial and mesenchymal differentiation. For practicing pathologists, identifying these transitional zones—particularly at invasive fronts or dedifferentiated components—provides valuable insight into tumor biology and expected clinical behavior.

Epithelial–mesenchymal transition (EMT) has significant clinical relevance, as it represents a biologic mechanism closely linked to tumor aggressiveness, metastatic potential, and therapeutic resistance. Beyond its molecular complexity, EMT provides an explanatory framework for many clinicopathologic observations routinely encountered in surgical pathology, particularly in tumors demonstrating infiltrative growth, dedifferentiation, and rapid clinical progression.

The acquisition of mesenchymal characteristics enables carcinoma cells to detach from the primary tumor mass, degrade extracellular matrix barriers, and migrate through surrounding tissues. EMT facilitates intravasation into lymphatic and vascular channels, thereby promoting metastatic dissemination. Importantly, metastatic colonization often involves partial reversal through mesenchymal–epithelial transition (MET), allowing tumor cells to re-establish epithelial growth at distant sites. This dynamic plasticity explains the morphologic heterogeneity frequently observed between primary tumors and metastatic lesions.[2] Histologically, tumors exhibiting EMT-associated features—such as tumor budding, single-cell invasion, and sarcomatoid transformation—consistently correlate with higher rates of lymph node involvement and distant metastasis. Thus, recognition of these morphologic patterns may provide indirect prognostic information even in routine hematoxylin–eosin examination.[6,7,18]

EMT is closely associated with loss of differentiation and progression toward high-grade malignancy. Dedifferentiated tumors often demonstrate reduced expression of lineage-specific markers, increased proliferative activity, and marked cellular pleomorphism. This process reflects enhanced cellular plasticity, allowing tumor cells to adapt to environmental stress and survive under adverse conditions such as hypoxia or therapeutic pressure.[6,7,9] In thyroid carcinoma, for example, progression from well-differentiated carcinoma to poorly differentiated carcinoma and ultimately anaplastic thyroid carcinoma illustrates a clinicopathologic continuum in which EMT plays a central role. These transitions are accompanied by aggressive clinical behavior and dramatically reduced survival, emphasizing the prognostic importance of EMT-related morphologic changes.[46]

Tumors undergoing EMT frequently exhibit resistance to conventional therapies, including chemotherapy, radiotherapy, and targeted treatments. EMT-associated cells demonstrate altered apoptotic signaling, increased DNA damage tolerance, and stem cell–like properties that contribute to treatment failure and disease recurrence. These biologic characteristics may explain why morphologically dedifferentiated tumors often respond poorly to standard therapeutic approaches.

Furthermore, EMT has been associated with modulation of the tumor immune microenvironment. Increased expression of immune checkpoint molecules, including PD-L1, has been reported in tumors demonstrating EMT-related phenotypes. This observation suggests a potential link between EMT and immune evasion, providing a biologic rationale for the use of immunotherapy in selected aggressive malignancies.[48]

For practicing pathologists, recognizing EMT-associated morphologic patterns may enhance clinicopathologic correlation and risk stratification. Although EMT itself is not currently a formal diagnostic category, its histologic footprints can alert pathologists to biologically aggressive tumor behavior. Reporting features such as tumor budding, dedifferentiation, and sarcomatoid components may therefore carry prognostic significance and assist multidisciplinary clinical decision-making.

Conclusions

Epithelial–mesenchymal transition (EMT) represents a fundamental biological mechanism driving tumor invasion, metastasis, and dedifferentiation across a wide spectrum of epithelial malignancies. Beyond its well-established molecular basis, EMT also manifests through recognizable histopathologic features observable in

routine practice, including loss of cellular cohesion, tumor budding, spindle cell transformation, infiltrative growth patterns, and progressive loss of differentiation. Rather than a binary process, EMT occurs along a dynamic continuum, explaining the morphologic heterogeneity commonly encountered within tumors and emphasizing the importance of careful evaluation of invasive and dedifferentiated components. Integration of morphologic assessment with immunohistochemical alterations further strengthens the link between tumor biology and histopathologic interpretation.

Clinically, EMT is strongly associated with aggressive tumor behavior, therapeutic resistance, and adverse outcomes, making its recognition relevant for prognostic assessment even in settings with limited access to advanced molecular testing. Understanding EMT provides pathologists with a unifying conceptual framework that connects traditional morphology with modern cancer biology, thereby enhancing clinicopathologic correlation. Incorporating EMT-related insights into routine diagnostic evaluation may ultimately improve prediction of tumor behavior and support multidisciplinary decision-making, reaffirming the central role of histopathology in the era of precision oncology.

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Declaration concerning generative AI and AI-augmented technologies in the compositional process

In the course of preparing this paper, the authors utilized ChatGPT to enhance readability and linguistic quality. Subsequent to utilizing this tool/service, the writers assessed and amended the information as necessary and assume complete accountability for the publication's content.

Declarations of competing interest

No potential competing interest was reported by the authors.

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