AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-1| 2026 Published: |30-01-2026

UDC: 616-006:616-091

PATHOLOGICAL-ANATOMICAL STAGES OF CANCER DEVELOPMENT AND METASTATIC PROGRESSION: BIOLOGICAL SIGNIFICANCE, MORPHOLOGICAL PATTERNS AND CLINICAL IMPLICATIONS

https://doi.org/10.2761/zenodo.18457425

Isroilov Asilbek Muhiddin ogli
Central Asian Medical University International Medical University Assistant in Pathological Anatomy , Burhoniddin Marg'inoniy Street-64, Phone: +998 95 485 00 70, Email: info@camuf.uz, Fergana, Uzbekistan1
E-mail: asilbekisroilov1994@gmail.com1

Abstract

Cancer represents a complex group of diseases characterized by uncontrolled cellular proliferation, invasive growth, and the capacity for distant dissemination. The pathological-anatomical evolution of tumors and their metastatic spread reflects a dynamic multistage biological process driven by genetic instability, epigenetic alterations, and tumor–microenvironment interactions. This article provides a comprehensive theoretical analysis of the pathological stages of carcinogenesis and metastasis, emphasizing their biological meaning, morphological characteristics, and clinical relevance. Cancer types, etiological factors, and molecular drivers are discussed as distinct components of tumor initiation. Metastasis is analyzed as a separate but interconnected phenomenon, with attention to its mechanisms, routes of spread, morphological patterns, and clinical course. Based on systematic analysis of peer-reviewed articles, dissertations, and authoritative scientific sources, this work synthesizes current theoretical knowledge on tumor progression and dissemination. The results highlight consistent morphological patterns that accompany malignant transformation, invasion, intravasation, circulation, extravasation, and colonization. Differences between primary tumor biology and metastatic lesions are clarified in terms of cellular behavior, microenvironmental dependence, and pathological anatomy. The discussion emphasizes how understanding these processes improves diagnostic accuracy, prognostic assessment, and therapeutic planning. This theoretical synthesis underscores the necessity of integrating pathological anatomy with molecular oncology for effective cancer control strategies.

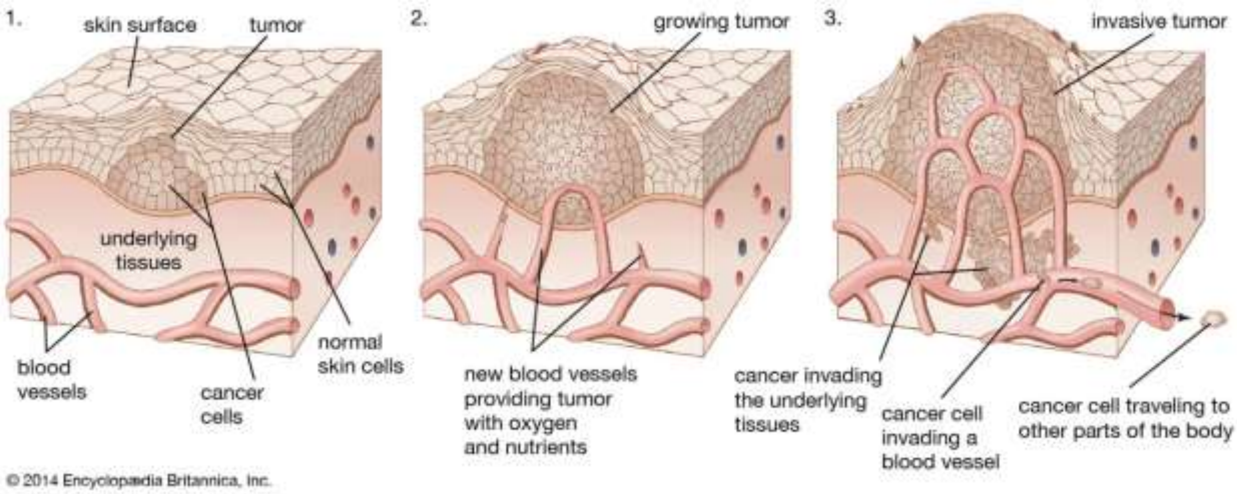
Keywords

AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-1| 2026 Published: |30-01-2026

Cancer, metastasis, pathological anatomy, carcinogenesis, tumor progression, invasion, dissemination, oncology, morphology, tumor microenvironment, staging, biology.

Introduction: Cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for millions of deaths annually and posing an enormous socioeconomic burden. Despite remarkable advances in molecular biology and targeted therapies, malignant tumors continue to challenge healthcare systems because of their heterogeneity, adaptability, and capacity for metastasis. From a pathological perspective, cancer is not a single disease but a broad spectrum of disorders united by common biological hallmarks: sustained proliferative signaling, resistance to cell death, genomic instability, and invasive behavior.

The pathological-anatomical approach occupies a central position in oncology. It provides direct visualization of structural changes occurring in tissues and organs during tumor development and progression. These morphological alterations reflect underlying molecular events and offer essential clues about tumor aggressiveness, differentiation status, and metastatic potential. Thus, pathological anatomy serves as a bridge between basic biological mechanisms and clinical manifestations.



1-Figure. Pathological–anatomical stages of tumor development and invasion. This schematic illustration demonstrates the sequential morphological changes occurring during tumor progression. The first stage shows localized abnormal cell proliferation within the epithelial layer, while the underlying tissue structure remains largely preserved. In the second stage, a growing tumor mass forms, accompanied by increased cellular proliferation and expansion toward deeper tissue layers. The third stage depicts an invasive carcinoma penetrating the basement membrane and infiltrating underlying tissues, with newly formed blood vessels supporting tumor growth and providing a pathway for dissemination.

These stages reflect the transition from localized neoplastic growth to invasive malignancy and highlight the structural basis of tumor progression and metastatic potential.

Carcinogenesis is a multistep process that transforms normal cells into malignant ones through accumulation of genetic and epigenetic alterations. These changes disrupt regulatory pathways governing cell cycle control, DNA repair, apoptosis, and differentiation. Over time, transformed cells acquire selective advantages that enable clonal expansion and formation of a primary tumor mass. However, the most life-threatening feature of cancer is not merely local growth but the ability to spread to distant organs.

Metastasis represents the final and most complex stage of malignant progression.

It involves a series of coordinated steps: detachment of tumor cells from the primary mass, invasion into surrounding tissues, entry into vascular or lymphatic channels, survival in circulation, exit into distant tissues, and establishment of secondary tumors. Each step requires specific biological adaptations and is accompanied by characteristic pathological changes.

Understanding the pathological-anatomical stages of cancer development and metastasis is essential for several reasons. First, these stages form the basis of tumor staging systems, which guide treatment selection and prognostic evaluation. Second, morphological patterns can reveal therapeutic targets and predict response to specific interventions. Third, knowledge of metastatic routes and organ tropism assists clinicians in surveillance and early detection of secondary lesions.

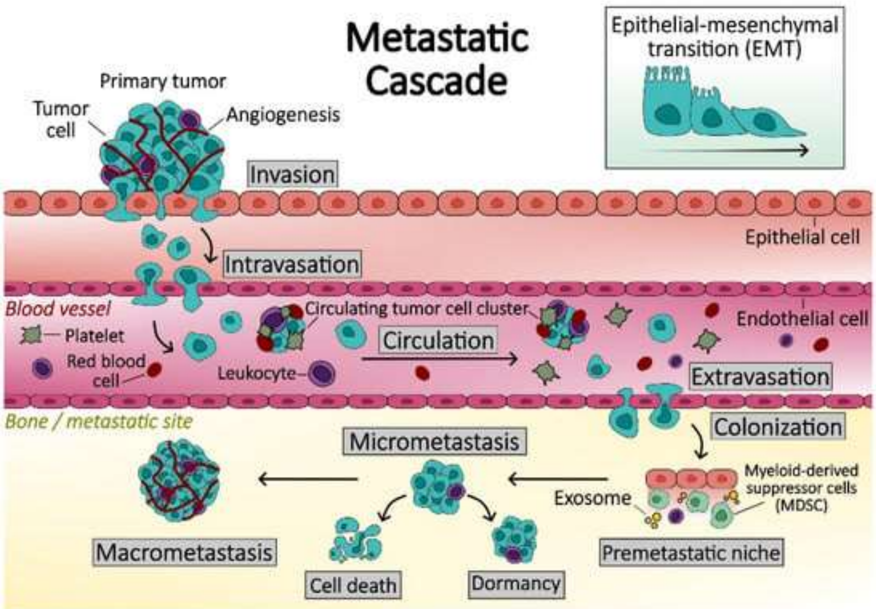


Figure 2. This figure illustrates the complex process of cancer metastasis. The metastatic process in cancer is a multi-stage event that involves the transformation and movement of cancer cells from the primary tumor site to secondary locations in

the body. The metastatic cascade begins with the tumor growth and angiogenesis, where new blood vessels form to supply nutrients to the tumor. Cancer cells then undergo epithelial–mesenchymal transition (EMT), a critical change that enhances their mobility and invasiveness, allowing them to breach the extracellular matrix and invade nearby tissues. The next phase, intravasation, sees these cells entering the bloodstream, where they can circulate as individual cells or clusters, interacting with blood components such as platelets and leukocytes. Upon reaching a distant site, the circulating tumor cells exit the bloodstream through extravasation. In the new tissue environment, these cells can remain dormant or progress to colonize, recruiting supporting cells such as myeloid-derived suppressor cells (MDSCs) and creating a premetastatic niche that facilitates the growth of micrometastasis into a full-blown macrometastasis. Throughout this journey, the interplay between cancer cells, the host's immune system, and the microenvironment of both the primary and metastatic sites are crucial for the successful establishment and growth of metastases.

Although numerous studies have explored molecular aspects of tumor biology, a comprehensive theoretical synthesis integrating pathological anatomy with biological significance remains indispensable. This article aims to present an in-depth analysis of cancer development and metastatic progression from a pathological-anatomical perspective. Special attention is given to defining cancer and its types, elucidating etiological factors, describing metastasis and its classifications, and comparing the biological and morphological characteristics of primary tumors and metastatic lesions.

By consolidating data from scientific literature and theoretical oncology, this work seeks to contribute to a deeper conceptual understanding of malignant disease and to support the continued refinement of diagnostic and therapeutic strategies.

Materials and Methods: This article is based on a structured theoretical analysis of scientific literature obtained from internationally recognized academic databases and repositories. Sources were identified through systematic searches of biomedical platforms containing peer-reviewed journals, doctoral dissertations, and authoritative textbooks in pathology and oncology. The search strategy focused on keywords related to carcinogenesis, tumor pathology, metastasis, invasion, morphological staging, and tumor biology.

Inclusion criteria consisted of publications presenting fundamental or applied research on pathological anatomy of tumors, biological mechanisms of cancer progression, and morphological correlates of metastasis. Priority was given to comprehensive reviews, meta-analyses, and seminal experimental studies that have shaped contemporary understanding of malignant disease. Dissertations and monographs were included when they provided detailed morphological descriptions or theoretical frameworks relevant to tumor development and dissemination.

Exclusion criteria encompassed non-scientific publications, case reports without analytical depth, and sources lacking clear methodological rigor. Only materials written in academically recognized languages and published in reputable outlets were considered.

Selected sources were subjected to qualitative content analysis. Core concepts, definitions, and theoretical models were extracted and organized into thematic categories: cancer definition and types, etiological factors, stages of carcinogenesis, mechanisms of metastasis, pathological-anatomical features of primary and secondary tumors, and biological significance of morphological changes.

No original experimental work was conducted. Instead, this article represents a conceptual synthesis of existing scientific knowledge. Data were interpreted in a descriptive and analytical manner, emphasizing consistency across studies and convergence of theoretical viewpoints.

The methodological approach aimed to ensure logical coherence, scientific accuracy, and conceptual clarity. Rather than focusing on numerical synthesis, the analysis prioritized integration of morphological, biological, and clinical perspectives to generate a holistic understanding of tumor progression.

Results:

Cancer as a Disease Entity: Cancer is defined as a group of diseases characterized by uncontrolled proliferation of abnormal cells capable of invading surrounding tissues and spreading to distant sites. Morphologically, malignant tumors differ from benign neoplasms by cellular atypia, high mitotic activity, architectural disorganization, and invasive growth patterns.

Types of Cancer:

Cancers are commonly classified according to tissue of origin:

Carcinomas: arising from epithelial tissues.

Sarcomas: originating from mesenchymal tissues.

Leukemias: malignancies of blood-forming tissues.

Lymphomas: tumors of lymphoid tissue.

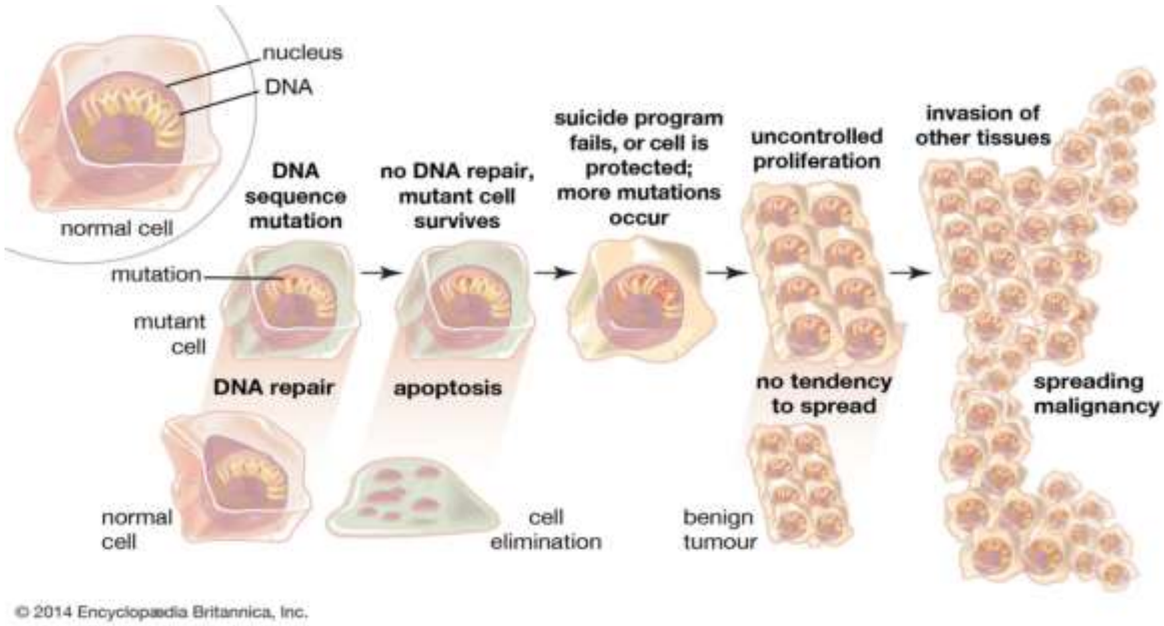
Neuroectodermal tumors: derived from nervous system elements.

Each type exhibits distinct morphological and biological characteristics.

Etiological Factors:

AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-1| 2026 Published: |30-01-2026

Cancer development is associated with a combination of intrinsic and extrinsic factors. Intrinsic factors include genetic predisposition and spontaneous mutations. Extrinsic factors encompass chemical carcinogens, ionizing radiation, ultraviolet exposure, infectious agents, and lifestyle-related influences. These factors induce DNA damage, epigenetic alterations, and genomic instability, initiating malignant transformation.



3-Figure. Molecular and cellular pathway of carcinogenesis and malignant transformation. This schematic diagram illustrates the sequential events leading from a normal cell to malignant tumor formation. Initially, a normal cell may acquire a DNA sequence mutation. Under physiological conditions, the cell either undergoes DNA repair or is eliminated through apoptosis. If DNA repair mechanisms fail and programmed cell death is bypassed, the mutant cell survives and accumulates additional genetic alterations. Progressive mutations disrupt regulatory pathways controlling cell cycle and survival, resulting in uncontrolled cellular proliferation. In some cases, this proliferation forms a benign tumor with no tendency to spread. However, continued genetic instability may lead to invasive growth and the ability of tumor cells to infiltrate surrounding tissues, culminating in spreading malignancy. This pathway highlights the critical roles of DNA damage, defective repair, and apoptosis evasion in cancer development.

Pathological Stages of Tumor Development:

1. Initiation: Irreversible genetic alteration in a single cell.

2. Promotion: Clonal expansion of initiated cells.

3. Progression: Acquisition of aggressive traits, including invasion and resistance to apoptosis.

Morphologically, progression is accompanied by increasing cellular atypia, pleomorphism, and loss of differentiation.

Metastasis: Definition and Mechanisms:

Metastasis is the formation of secondary tumor foci at sites distant from the primary tumor. It occurs through lymphatic spread, hematogenous dissemination, or transcoelomic implantation.

Types of Metastasis

Lymphogenous metastasis

Hematogenous metastasis

Implantation metastasis

Each route produces characteristic distribution patterns.

Clinical Course:

Metastasis often correlates with advanced disease stage and poor prognosis. Clinically, patients may present with organ-specific symptoms depending on metastatic localization.

Morphological Features of Metastatic Lesions

Metastatic tumors typically resemble the primary tumor histologically but may show additional features of dedifferentiation and increased aggressiveness.

Discussion: Cancer development and metastatic progression represent a continuum of biological transformation rather than discrete and isolated events. From a pathological-anatomical standpoint, malignant disease evolves through successive structural and functional alterations that mirror underlying molecular reprogramming. These changes are not merely passive reflections of genetic damage but active expressions of cellular adaptation to selective pressures within the tissue microenvironment. Consequently, pathological anatomy serves not only as a descriptive discipline but also as an interpretative framework for understanding tumor biology.

AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-1| 2026 Published: |30-01-2026

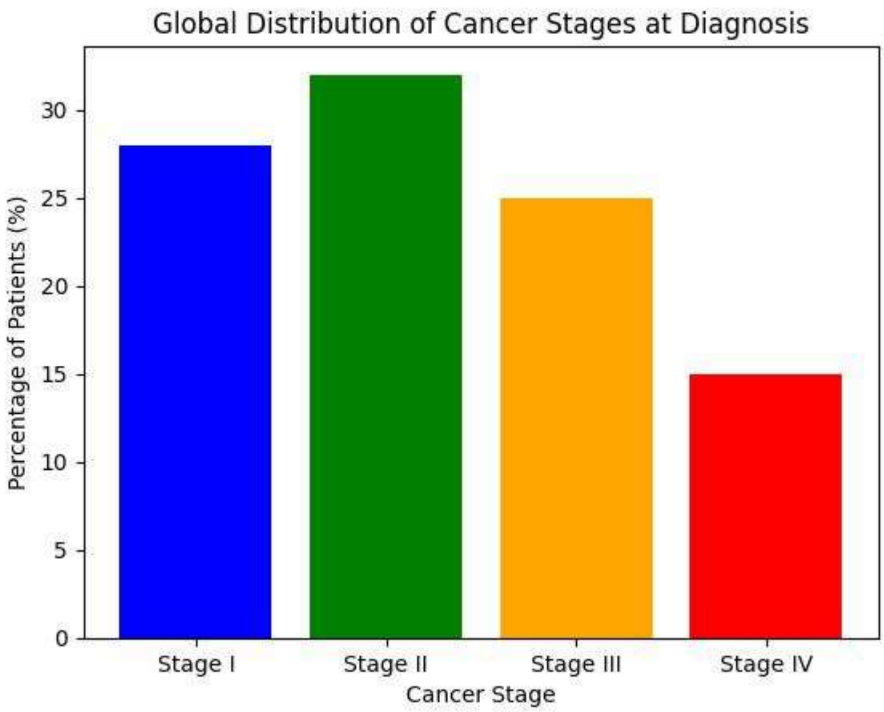


Figure 4. Global Distribution of Cancer Stages at Diagnosis. This bar chart illustrates the approximate percentage distribution of patients diagnosed at different cancer stages worldwide. Early-stage detection (Stages I–II) accounts for a higher proportion of cases compared to advanced stages, reflecting the growing impact of screening and early diagnostic strategies.

One of the central observations in cancer pathology is the gradual loss of normal tissue architecture. Early neoplastic lesions often preserve partial structural organization, while advanced tumors exhibit complete architectural disarray. This morphological progression parallels the accumulation of genetic instability and epigenetic deregulation. Cells acquire increasing degrees of pleomorphism, nuclear atypia, hyperchromasia, and abnormal mitotic figures. Such features are not random; they reflect profound disturbances in chromatin organization, DNA repair mechanisms, and cell cycle regulation. Therefore, morphological atypia should be interpreted as a visible manifestation of molecular chaos.

Tumor heterogeneity is another hallmark that becomes increasingly evident during progression. Even within a single tumor mass, multiple subclones with distinct morphological and biological characteristics may coexist. Pathologically, this heterogeneity appears as regions of varying differentiation, necrosis, fibrosis, and vascularization. Biologically, it corresponds to clonal evolution driven by selective advantages. Subclones that proliferate more rapidly, resist apoptosis, or adapt better to hypoxia gradually dominate the tumor population. This evolutionary perspective explains why cancers often become more aggressive over time and why therapeutic resistance frequently emerges.

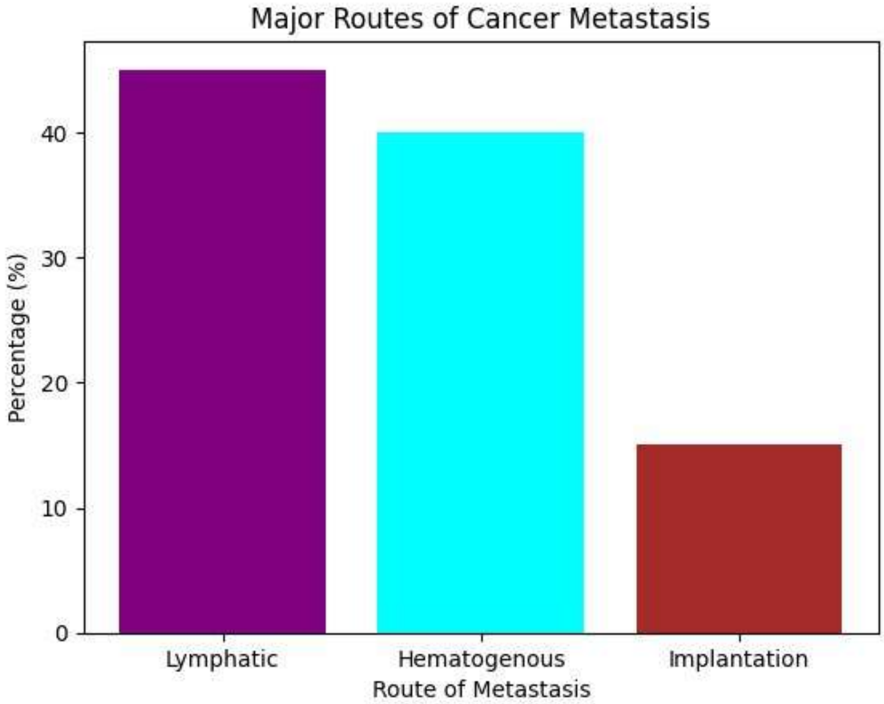


Figure 5. Major Routes of Cancer Metastasis. This diagram shows the relative contribution of lymphatic, hematogenous, and implantation pathways in metastatic spread. Lymphatic dissemination represents the most frequent route, followed closely by hematogenous spread, while implantation metastasis is less common.

Invasion represents a pivotal transition from localized growth to aggressive behavior. Pathologically, invasion is characterized by breach of basement membranes and infiltration of surrounding stroma. This process requires coordinated degradation of extracellular matrix components, loss of cell–cell adhesion, and acquisition of motile phenotypes. Morphological evidence of invasion includes irregular tumor borders, single-cell infiltration, and stromal desmoplasia. These features reflect profound changes in cytoskeletal organization and cell surface molecule expression. Thus, invasion is both a structural and biological transformation, signifying the tumor's shift from tissue-restricted proliferation to spatial expansion.

Metastasis constitutes the most complex stage of malignant progression and remains the principal cause of cancer-related mortality. Pathological anatomy demonstrates that metastasis is not a single event but a cascade of sequential steps, each associated with distinct morphological correlates. Detachment of tumor cells from the primary mass is often accompanied by reduced intercellular cohesion. Entry into lymphatic or blood vessels can be visualized as intravascular tumor emboli. At distant sites, metastatic deposits initially appear as microscopic clusters that may remain dormant or progress to clinically significant lesions.

A striking feature of metastatic tumors is their dual identity. On one hand, they retain histological characteristics of the primary tumor, allowing determination of tissue origin. On the other hand, they often exhibit additional features of dedifferentiation, increased mitotic activity, and necrosis. This duality reflects the selective pressures encountered during dissemination.

Only cells capable of surviving detachment, mechanical stress, immune surveillance, and foreign microenvironments can establish metastases. Consequently, metastatic cells represent a highly selected subpopulation with enhanced adaptability.

The biological distinction between primary tumor growth and metastatic colonization is of major conceptual importance. Primary tumors are largely shaped by interactions within their tissue of origin, whereas metastatic lesions must adapt to entirely new ecological niches. Pathologically, this difference is reflected in variations in stromal composition, vascular patterns, and inflammatory responses. Biologically, it implies that metastatic competence is not an inevitable property of all tumor cells but a specialized phenotype acquired by a minority of cells.

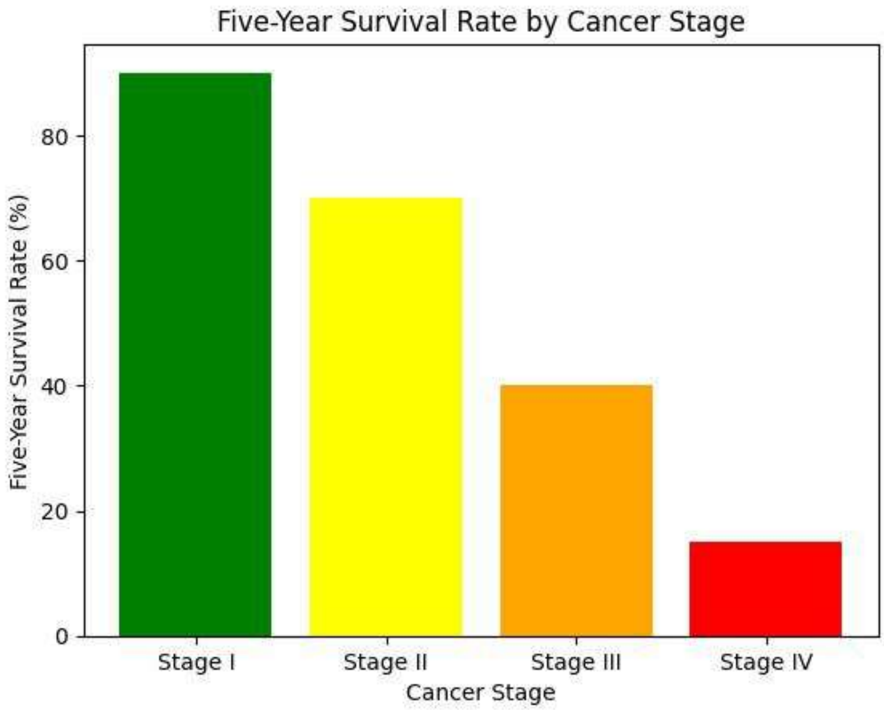


Figure 3. Five-Year Survival Rate by Cancer Stage. This figure demonstrates the inverse relationship between cancer stage and five-year survival rate. Survival is highest in Stage I disease and declines progressively with advancing stage, emphasizing the prognostic significance of early detection.

The tumor microenvironment emerges as a central determinant of both primary growth and metastasis. Fibroblasts, immune cells, endothelial cells, and extracellular matrix components collectively form a dynamic ecosystem.

Pathological examination frequently reveals dense fibrotic stroma, abnormal vasculature, and inflammatory infiltrates surrounding tumor cells. These features are not merely reactive; they actively influence tumor behavior. For example, hypoxic regions promote angiogenesis and select for cells with altered metabolic pathways. Inflammatory mediators can stimulate proliferation and facilitate invasion. Thus, pathological anatomy captures the visible footprint of complex cellular crosstalk.

From a clinical standpoint, the pathological-anatomical stages of cancer and metastasis underpin tumor staging systems. Tumor size, depth of invasion, lymph node involvement, and presence of distant metastases remain among the most powerful predictors of outcome. The correlation between morphological stage and prognosis underscores the biological reality that cancer aggressiveness increases as structural abnormalities accumulate. Early-stage tumors, confined to their tissue of origin, are often curable. Advanced-stage tumors with extensive invasion and metastasis are significantly more difficult to control.

Another important implication of pathological anatomy is its role in guiding therapeutic strategies. Surgical resection depends on accurate assessment of tumor margins and depth of invasion. Radiotherapy planning relies on knowledge of anatomical spread. Systemic therapies are influenced by tumor grade and metastatic burden. Thus, morphological evaluation directly shapes clinical decision-making.

The comparison between cancer development and metastasis reveals both continuity and divergence. Both processes involve genetic instability, clonal selection, and adaptation. However, cancer development primarily reflects local evolutionary dynamics, whereas metastasis represents a form of biological colonization. This distinction explains why some tumors grow extensively without metastasizing, while others metastasize early despite relatively small primary size

Biologically, the capacity for metastasis confers a decisive survival advantage at the level of the tumor population but is catastrophic for the host organism. From an evolutionary perspective, metastatic competence can be viewed as the ultimate expression of malignant fitness. Pathologically, it manifests as widespread structural disruption across multiple organs.

In summary, pathological anatomy provides a macroscopic and microscopic narrative of cancer biology. Each morphological change corresponds to a functional adaptation. By interpreting these changes within a biological framework, clinicians and researchers gain deeper insight into tumor behavior. This integrated understanding is essential for developing more effective diagnostic, prognostic, and therapeutic approaches.

Conclusion: Cancer development and metastasis represent interconnected yet distinct biological processes manifested through characteristic pathological-anatomical stages. Primary tumor formation reflects progressive genetic and epigenetic alterations leading to uncontrolled growth and tissue invasion. Metastasis embodies the culmination of malignant evolution, requiring complex cellular adaptations and microenvironmental interactions. Differences between primary and metastatic tumors are evident in both biological behavior and morphological structure. A thorough understanding of these processes enhances diagnostic precision, prognostic assessment, and therapeutic decision-making. Integrating morphological analysis with modern molecular insights remains essential for advancing oncology practice and improving patient outcomes.

REFERENCES:

1. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. Cell, 144(5), 646–674.

2. Hanahan, D. (2022). Hallmarks of cancer: New dimensions. Cancer Discovery, 12(1), 31–46.

3. Kumar, V., Abbas, A. K., Aster, J. C., & Turner, J. R. (2021). Robbins and Cotran Pathologic Basis of Disease (11th ed.). Elsevier.

4. Weinberg, R. A. (2014). The Biology of Cancer (2nd ed.). Garland Science.

5. DeVita, V. T., Lawrence, T. S., & Rosenberg, S. A. (2019). Cancer: Principles and Practice of Oncology (11th ed.). Wolters Kluwer.

6. Majno, G., & Joris, I. (2004). Cells, Tissues, and Disease. Oxford University Press.

7. Fink, S. L., & Cookson, B. T. (2005). Apoptosis, pyroptosis, and necrosis. Infection and Immunity, 73(4), 1907–1916.

8. Kerr, J. F. R., Wyllie, A. H., & Currie, A. R. (1972). Apoptosis. British Journal of Cancer, 26, 239–257.

9. Kroemer, G., et al. (2009). Classification of cell death. Cell Death & Differentiation, 16(1), 3–11.

10. Tait, S. W. G., & Green, D. R. (2010). Mitochondria and cell death. Cold Spring Harbor Perspectives in Biology, 2(9), a004671.

10. Cotran, R. S., Kumar, V., & Collins, T. (1999). Pathologic Basis of Disease. Saunders.

11. Ergashev, B. (2025). Advances in oral health: Prevention, treatment, and systemic implications. American Journal of Education and Learning, 3(3), 1108–1114.

12. Hacker, G. (2000). The morphology of apoptosis. Cell and Tissue Research, 301(1), 5–17.

13. Leist, M., & Jäättelä, M. (2001). Four deaths and a funeral. Nature Reviews Molecular Cell Biology, 2, 589–598.

14. Ergashev, B. (2025). Psychological support for cancer patients. ИКРО журнал, 15(1), 164–167.

15. Thompson, C. B. (1995). Apoptosis in development. Science, 267(5203), 1456–1462.

16. Ergashev, B. J. Oglu. (2025). Kennedy classification: Its significance. Tabib, 1(1), 1–7.

17. Adams, J. M., & Cory, S. (2007). Bcl-2-regulated apoptosis. Oncogene, 26, 1324–1337.

18. Fulda, S., & Debatin, K. M. (2006). Extrinsic apoptosis pathways. Oncogene, 25, 4798–4811.

19. Ergashev, B. (2025). Etiology and pathogenesis of acute periodontitis. Modern Science and Research, 4(5), 596–601.

20. Hotchkiss, R. S., et al. (2009). Cell death in disease. New England Journal of Medicine, 361, 1570–1583.

21. Ergashev, B. (2025). The impact of energy drink consumption on the development and mineralization of teeth in adolescents. Академические исследования в современной науке, 4(31), 52–55.

22. Rock, K. L., et al. (2010). The sterile inflammatory response. Annual Review of Immunology, 28, 321–342.

23. Nicholson, D. W. (1999). Caspase structure and function. Cell Death & Differentiation, 6, 1028–1042.

24. Ergashev, B. (2025). Optimizing non-removable orthodontic treatment through individualized therapeutic programs for irreversible malocclusions. Естественные науки в современном мире, 4(7), 60–62.

25. Baines, C. P. (2010). The mitochondrial permeability transition pore. Journal of Molecular and Cellular Cardiology, 46(6), 850–857.