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HISTOPATHOLOGICAL CHARACTERISTICS OF THE TUMOR MICROENVIRONMENT AND THEIR ROLE IN CANCER PROGRESSION

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ABSTRACT Background: The tumor microenvironment (TME) represents a complex biological system composed of malignant cells, immune infiltrates, cancer-associated fibroblasts, endothelial cells, extracellular matrix components, and soluble signaling molecules. Increasing evidence demonstrates that the structural and functional organization of these components contributes substantially to tumor growth, local invasion, metastatic dissemination, and therapeutic resistance.

Objective: To analyze the major histopathological characteristics of the tumor microenvironment, evaluate their relationships with malignant progression, and examine contemporary diagnostic approaches for assessing tumor–stromal interactions.

Materials and Methods: A narrative review of international scientific publications, original histopathological investigations, clinical studies, and contemporary molecular research available through November 2026 was conducted. Particular attention was given to tumor-infiltrating lymphocytes, cancer-associated fibroblasts, extracellular matrix remodeling, angiogenesis, hypoxia, tumor budding, and spatial organization of cellular populations.

Results: Published evidence indicates that the composition and spatial distribution of immune and stromal cells influence tumor behavior and clinical outcomes. An international study involving 2,681 patients with colon cancer demonstrated the prognostic significance of the Immunoscore, while a pooled analysis of 3,771 patients with breast cancer identified associations between stromal lymphocytic infiltration and response to neoadjuvant chemotherapy. Recent advances in spatial transcriptomics and artificial intelligence have further demonstrated that distinct cellular neighborhoods within tumors are associated with progression, prognosis, and response to immunotherapy.

Conclusion: Histopathological evaluation of the tumor microenvironment provides clinically relevant information beyond conventional assessment of malignant cell morphology. Integration of routine histology with immunohistochemistry, spatial molecular techniques, and digital pathology may improve prognostic stratification and support the development of personalized oncological treatment strategies.

Keywords: tumor microenvironment, histopathology, cancer progression, tumor-infiltrating lymphocytes, cancer-associated fibroblasts, extracellular matrix, angiogenesis, tumor budding, immune evasion, spatial transcriptomics.

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INTRODUCTION

Malignant tumors are complex biological structures whose development and progression depend not only on the genetic and molecular abnormalities of neoplastic cells but also on their interactions with surrounding nonmalignant tissues. Traditionally, pathological examination of malignant neoplasms has concentrated on cellular atypia, nuclear pleomorphism, mitotic activity, tumor differentiation, necrosis, and the extent of local tissue invasion. These characteristics remain fundamental for establishing a diagnosis and determining histological grade. However, contemporary oncological research increasingly recognizes that the biological behavior of tumors is also influenced by the structural organization, cellular composition, and functional activity of the surrounding microenvironment. The tumor microenvironment consists of malignant epithelial or mesenchymal cells interacting with fibroblasts, immune cells, endothelial cells, pericytes, extracellular matrix proteins, and soluble molecular mediators. These components participate in dynamic processes that influence cell proliferation, angiogenesis, immune surveillance, metabolic adaptation, invasion, and metastatic dissemination. Hanahan (2022) emphasized that the characteristics of malignant progression arise from interconnected biological mechanisms involving both tumor-intrinsic alterations and reciprocal interactions with the surrounding tissue environment [1]. Consequently, the tumor should be regarded as an evolving tissue ecosystem rather than an isolated accumulation of genetically altered cells. This concept has important implications for pathological anatomy because routine histological preparations contain visible evidence of tumor–stromal interactions, including inflammatory infiltration, fibrotic stromal reactions, abnormal vascular structures, necrotic regions, and morphological changes at invasive tumor margins. These findings may provide information concerning tumor aggressiveness and prognosis that cannot be obtained through evaluation of malignant cells alone.

The structural organization of the tumor microenvironment varies substantially between different cancer types and even among separate regions of the same neoplasm. Some tumors demonstrate dense lymphocytic infiltration and relatively limited stromal expansion, whereas others are characterized by extensive desmoplasia, poorly organized blood vessels, hypoxic areas, and exclusion of cytotoxic immune cells from malignant epithelial compartments. Such differences reflect complex interactions between tumor-derived signals and surrounding stromal populations. Cancer-associated fibroblasts contribute to extracellular matrix production and remodeling, while immune cells may exert either antitumor or tumor-promoting effects depending on their functional characteristics and anatomical distribution. Endothelial abnormalities can influence oxygen delivery, metabolic conditions, and the transport of therapeutic agents. Meanwhile, extracellular matrix organization affects tissue stiffness, cellular adhesion, and the mechanical signals associated with invasive behavior. Sahai and colleagues (2020) described cancer-associated fibroblasts as functionally heterogeneous stromal populations that participate in matrix remodeling, immune regulation, and communication with malignant cells [2]. Similarly, Fridman and colleagues (2017) emphasized that the prognostic significance of tumor-

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associated immunity depends not simply on the presence of inflammatory cells but also on their functional identity, density, and spatial distribution [3]. These findings demonstrate that conventional morphological observations may reflect underlying molecular processes relevant to malignant progression. Therefore, contemporary histopathological evaluation increasingly incorporates both the characteristics of neoplastic cells and the biological organization of the surrounding tissue environment.

Recent technological advances have substantially expanded the possibilities for analyzing tumor microenvironments. Immunohistochemistry permits the identification of selected immune-cell populations, stromal markers, endothelial structures, and proteins involved in cellular signaling. Digital pathology enables quantitative examination of tissue architecture, while multiplex immunofluorescence and spatial transcriptomics provide information about the anatomical distribution and interactions of different cellular populations. These methods allow researchers to investigate whether immune cells penetrate malignant epithelial structures, accumulate near invasive margins, or remain separated from tumor cells by fibrotic stromal barriers. In 2026, Li and colleagues published a pan-cancer spatial transcriptomic investigation involving 373 tissue samples from 12 cancer types and identified 56 local cellular programs and 13 recurrent spatial niches associated with distinct biological characteristics [12]. During the same year, another investigation published in Cell demonstrated that artificial intelligence could infer aspects of tumor spatial organization from conventional hematoxylin-and-eosin-stained preparations [11]. Such developments suggest that routine histopathological examination may become increasingly connected with molecular and computational methods for studying cancer biology. Nevertheless, the clinical interpretation of these technologies requires careful validation because tumor microenvironments are highly heterogeneous, and findings obtained from one cancer type cannot necessarily be generalized to another. The aim of the present study is to analyze the histopathological characteristics of the tumor microenvironment, evaluate their involvement in cancer progression and metastatic behavior, and examine contemporary approaches for integrating morphological assessment with molecular and spatial diagnostic technologies.

MATERIALS AND METHODS

The present study was conducted as a narrative review of international scientific literature concerning the histopathological organization of the tumor microenvironment and its relationship with malignant progression. Relevant peer-reviewed publications available through November 2026 were examined, including original histopathological studies, multicenter clinical investigations, consensus recommendations, experimental research, and contemporary scientific reviews. Particular attention was given to publications in Cancer Discovery, Nature Reviews Cancer, Nature Reviews Clinical Oncology, Nature Medicine, Science, The Lancet, The Lancet Oncology, Modern Pathology, Cell, and Cell Reports Medicine. The analytical framework focused on the morphological and biological characteristics of tumor-associated immune infiltrates, cancer-associated fibroblasts, extracellular matrix remodeling, angiogenesis, hypoxia, tumor budding, and the spatial relationships among different cell populations. Studies employing conventional hematoxylin-and-eosin staining, immunohistochemistry, multiplex

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imaging, digital histopathology, and spatial molecular profiling were considered relevant. The available evidence was evaluated using descriptive and comparative analytical methods, with emphasis on the relationship between histological findings, mechanisms of tumor progression, clinical prognosis, and therapeutic response. Particular consideration was given to standardized approaches for evaluating tumor-infiltrating lymphocytes and tumor budding, as well as studies investigating the prognostic significance of immune-cell distribution and tumor–stromal architecture. Findings derived from different cancer types were interpreted according to their original clinical and methodological contexts. No original patient recruitment, tissue sampling, microscopic examination, laboratory experimentation, or independent statistical meta-analysis was performed. Accordingly, the results represent a critical synthesis of previously published evidence rather than findings obtained from an independent histopathological investigation.

RESULTS

The reviewed scientific literature demonstrates that the tumor microenvironment contains a heterogeneous population of immune cells whose distribution and functional characteristics can influence malignant progression. Tumor-infiltrating lymphocytes are among the most extensively investigated morphological components because they provide visible evidence of the interaction between neoplastic tissue and the host immune system. Cytotoxic CD8-positive T lymphocytes may contribute to the recognition and elimination of malignant cells, while CD4-positive T-cell populations include functionally distinct subsets that can support or regulate immune responses. Regulatory T cells, macrophages, dendritic cells, B lymphocytes, and other immune populations participate in complex interactions that may either restrict tumor progression or facilitate immune evasion. Importantly, the prognostic significance of immune infiltration depends on the type and location of immune cells rather than their total abundance alone. Galon and colleagues (2006) demonstrated that the type, density, and localization of immune cells within colorectal tumors were strongly associated with clinical outcomes [4]. Their investigation showed that immune-cell populations situated in both the tumor center and invasive margin provided important prognostic information. Subsequent research expanded these observations through the development of standardized immunological assessment methods. In an international validation study involving 2,681 patients with stage I–III colon cancer, Pagès and colleagues (2018) evaluated the prognostic performance of the consensus Immunoscore, which incorporates the densities of CD3-positive and CD8-positive T lymphocytes in the tumor center and invasive margin [5]. In the training cohort of 700 patients, five-year recurrence rates were approximately 8% among patients with high Immunoscore, 19% among those with intermediate Immunoscore, and 32% among those with low Immunoscore. These findings indicated that the spatial organization of antitumor immune responses provides prognostic information that complements conventional pathological staging. Nevertheless, the clinical relevance of immune infiltration is tumor-specific, and high lymphocyte density does not uniformly predict favorable outcomes in every malignancy.

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The importance of lymphocytic infiltration has also been demonstrated in breast cancer, where stromal tumor-infiltrating lymphocytes have been investigated as potential prognostic and predictive biomarkers. Salgado and colleagues (2015) developed recommendations for the standardized morphological assessment of tumor-infiltrating lymphocytes in breast cancer using hematoxylin-and-eosin-stained preparations [7]. The proposed methodology emphasizes evaluation of mononuclear inflammatory cells within the stromal compartment of the invasive tumor, while excluding areas affected by necrosis, artifacts, and other conditions that may interfere with interpretation. This approach provides a reproducible framework for studying immune infiltration using routine pathological material. Denkert and colleagues (2018) subsequently performed a pooled analysis involving 3,771 patients with breast cancer treated with neoadjuvant chemotherapy in six randomized clinical trials [6]. The investigators demonstrated associations between stromal lymphocytic infiltration and pathological complete response, with the direction and magnitude of the relationship varying across molecular breast cancer subtypes. In triple-negative breast cancer, pathological complete response occurred in approximately 31% of patients with low lymphocytic infiltration and 50% of those with high infiltration. In HER2-positive tumors, the corresponding proportions were approximately 32% and 48%. These findings suggest that immune-cell infiltration may reflect biological characteristics relevant to therapeutic responsiveness, particularly in selected breast cancer subtypes. However, lymphocyte abundance should not be interpreted independently of tumor subtype, molecular markers, and established clinicopathological factors. Furthermore, the spatial arrangement of immune cells may influence their functional effectiveness, since lymphocytes concentrated in peripheral stromal regions may not interact with malignant epithelial cells in the same manner as immune cells infiltrating tumor nests. Binnewies and colleagues (2018) described the tumor immune microenvironment as a dynamic system in which immune recognition, stromal barriers, inhibitory signaling pathways, and cellular interactions determine the effectiveness of antitumor responses [10]. These observations reinforce the importance of integrating quantitative immune-cell assessment with spatial and morphological interpretation.

Cancer-associated fibroblasts represent another major component of the tumor microenvironment and contribute substantially to the histopathological characteristics of malignant tissues. In many carcinomas, fibroblast activation is associated with increased production of collagen, fibronectin, and other extracellular matrix components, resulting in varying degrees of stromal fibrosis or desmoplasia. Histologically, desmoplastic reactions may appear as dense collagenous tissue containing elongated fibroblastic cells, irregular extracellular matrix fibers, and variable inflammatory or vascular components. Such stromal changes are particularly prominent in several epithelial malignancies, including pancreatic ductal adenocarcinoma, breast carcinoma, and selected gastrointestinal cancers. Fibroblasts interact with malignant cells through growth factors, cytokines, extracellular vesicles, and direct contact with matrix structures, thereby influencing cellular proliferation, differentiation, migration, and invasion. Transforming growth factor-beta, platelet-derived growth factor, and other

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signaling molecules may participate in fibroblast activation and extracellular matrix remodeling. Activated fibroblast populations may express markers such as alpha-smooth muscle actin, fibroblast activation protein, and platelet-derived growth factor receptors, although these proteins are not individually specific for all cancer-associated fibroblast populations. Sahai and colleagues (2020) emphasized that cancer-associated fibroblasts demonstrate substantial functional heterogeneity and may participate in both tumor-promoting and tumor-restricting processes [2]. Consequently, the presence of increased fibroblast density does not automatically establish aggressive biological behavior. The effects of stromal activation depend on fibroblast phenotype, tumor type, matrix composition, and interactions with immune and malignant cells. From a pathological perspective, assessment of stromal characteristics may provide valuable complementary information regarding tumor architecture and the biological conditions supporting malignant progression. Nevertheless, reliable interpretation requires recognition that conventional histological morphology does not fully distinguish the functional diversity of fibroblast populations.

Extracellular matrix remodeling represents an important structural mechanism through which the tumor microenvironment influences invasion and metastatic dissemination. The extracellular matrix contains collagen fibers, laminins, fibronectin, proteoglycans, and other macromolecules that provide mechanical support while also regulating cellular adhesion, migration, and biochemical signaling. During malignant progression, the organization of these components may undergo substantial changes, resulting in increased matrix density, altered fiber orientation, abnormal tissue stiffness, and disruption of normal anatomical barriers. Malignant cells and stromal populations may produce enzymes involved in extracellular matrix degradation and remodeling, including matrix metalloproteinases. These processes facilitate movement of cancer cells through surrounding tissues and may contribute to vascular or lymphatic invasion. Integrin-mediated interactions between tumor cells and matrix proteins also activate intracellular pathways regulating cytoskeletal organization, survival, and migration. The resulting mechanical and biochemical signals can influence invasive behavior independently of changes in the genetic composition of malignant cells. Histologically, these processes may be reflected by irregular invasive margins, disruption of normal tissue boundaries, stromal fibrosis, and isolated malignant cells extending into surrounding tissue. One of the most clinically relevant manifestations is tumor budding, defined in colorectal cancer as the presence of individual malignant cells or small clusters containing up to four tumor cells at the invasive front. Lugli and colleagues (2017) established international consensus recommendations for assessing tumor budding, including evaluation within a standardized hotspot area of 0.785 mm^2 [8]. The consensus recognized tumor budding as a prognostic factor associated with lymph node metastasis in early colorectal cancer and survival in stage II disease. These observations demonstrate that morphological changes at the tumor–stromal interface may provide important evidence of invasive potential. However, tumor budding should not be interpreted as a direct measurement of epithelial–mesenchymal transition, because the relationship between morphological dissociation and underlying cellular plasticity is complex.

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Angiogenesis represents another fundamental component of malignant progression because expanding tumors require access to oxygen, nutrients, and mechanisms for metabolic waste removal. Tumor-associated blood vessels frequently demonstrate structural and functional abnormalities, including irregular branching, heterogeneous luminal dimensions, incomplete supporting cell coverage, and increased vascular permeability. Such abnormalities may contribute to inefficient perfusion and the development of hypoxic regions within malignant tissues. Hypoxia can influence tumor-cell metabolism, inflammatory signaling, angiogenic mediator production, and susceptibility to therapy. Hypoxia-inducible factors participate in the regulation of genes associated with metabolic adaptation, vascular growth, and cellular survival under reduced oxygen availability. Vascular endothelial growth factor is among the most extensively investigated mediators of tumor-associated angiogenesis and contributes to endothelial proliferation and vascular remodeling. From a histopathological perspective, angiogenic activity may be evaluated using markers such as CD31 or CD34 in selected research and diagnostic settings, while necrotic regions and abnormal vascular architecture provide indirect evidence of disturbances in tissue oxygenation. Jain (2005) proposed the concept of vascular normalization, emphasizing that selected antiangiogenic interventions may temporarily improve vascular organization and function rather than exclusively destroying tumor blood vessels [9]. This concept has important implications for treatment because abnormal perfusion may limit the delivery of chemotherapeutic agents and influence the distribution of immune cells within malignant tissues. However, microvessel density alone does not fully characterize vascular function, and hypoxia cannot be reliably determined through routine morphology without appropriate clinical and molecular context. The biological effects of angiogenesis also differ according to tumor type and the interactions between endothelial cells, stromal populations, and immune infiltrates.

The interaction between immune regulation, stromal remodeling, and tumor metabolism contributes to the development of local conditions favorable for immune evasion. Malignant cells may alter their metabolic activity, consume substantial quantities of glucose and other nutrients, and release metabolites that influence surrounding immune populations. In some tumors, increased glycolytic metabolism contributes to local lactate accumulation and extracellular acidification, which may modify the functional properties of lymphocytes, macrophages, and stromal cells. Hypoxia can further influence immune-cell recruitment and differentiation, while dense extracellular matrix structures may restrict the movement of cytotoxic lymphocytes toward malignant epithelial compartments. Tumor-associated macrophages represent an important component of this environment because they participate in inflammatory signaling, matrix remodeling, phagocytosis, angiogenesis, and interactions with adaptive immunity. Although macrophages are frequently divided into broadly inflammatory and alternatively activated phenotypes in experimental studies, human tumor-associated macrophages display a wider range of functional states that cannot be fully characterized using a single molecular marker. Markers such as CD68 and CD163 may assist with the identification and characterization of macrophage populations, but their expression does not independently establish a uniformly tumor-promoting

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function. Fridman and colleagues (2017) emphasized that the organization of immune populations within tumors influences both prognosis and therapeutic response [3]. More recent research has demonstrated that the same immune-cell population may be associated with different clinical outcomes depending on its spatial relationships with malignant cells and other components of the microenvironment. Consequently, effective histopathological characterization requires consideration of immune-cell location, interaction networks, and tissue architecture rather than relying exclusively on individual cell counts.

The importance of spatial organization was further demonstrated by Li and colleagues in a pan-cancer investigation published in Cell Reports Medicine in 2026 [12]. The researchers analyzed spatial transcriptomic data from 373 tumor samples representing 12 cancer types and identified 56 local cellular programs together with 13 recurrent spatial niches. Their findings demonstrated that gene expression patterns in tumor cells and macrophages were strongly influenced by their location within the tissue environment. In particular, macrophage-rich niches located near malignant cells were associated with unfavorable prognosis and resistance to immunotherapy, whereas selected niches characterized by macrophage proximity to immune-cell populations demonstrated more favorable associations with survival and therapeutic response. These findings indicate that biological interpretation of immune infiltration depends on the anatomical relationships among different cellular populations. Another major investigation published by Yuchen Li and colleagues in Cell in 2026 developed an artificial intelligence platform known as CANVAS for inferring spatial tumor characteristics from routine hematoxylin-and-eosin-stained histological preparations [11]. The platform was developed using an atlas containing more than 18 million cells characterized by multiplex spatial proteomics from 457 patients with non-small-cell lung cancer. The investigators identified ten reproducible cellular neighborhoods and subsequently evaluated the approach using histopathological data from more than 5,000 patients across nine cancer types. The study demonstrated the feasibility of predicting biologically relevant aspects of tumor organization from conventional morphological material and identified associations with prognostic classification and immunotherapy outcomes. However, these computational predictions were developed and evaluated within defined research datasets, and their use as independent clinical decision-making tools requires further prospective validation. Together, these investigations demonstrate that tumor microenvironment assessment is evolving from descriptive morphology toward integrated spatial characterization of cellular ecosystems.

The reviewed evidence further indicates that tumor microenvironment characteristics may contribute to treatment resistance through several overlapping mechanisms. Dense stromal structures may influence the diffusion and distribution of therapeutic agents, while abnormal vascular networks may create heterogeneous treatment exposure within different regions of the same tumor. Hypoxia and altered metabolic conditions may modify cellular sensitivity to radiation and systemic therapy, whereas immunosuppressive signaling can reduce the effectiveness of antitumor immune responses. Some tumors demonstrate increased expression of immune checkpoint-related molecules, while others possess

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structural environments in which cytotoxic lymphocytes are physically or functionally excluded from direct interactions with malignant cells. These characteristics may influence the response to immune checkpoint inhibitors, although their predictive significance varies between cancer types and treatment settings. The relationship between tumor morphology and immune response is therefore not adequately captured by a single histopathological parameter. Aguilar-Cazares and colleagues (2026) described the tumor microenvironment as a complex network of stromal, immune, metabolic, and extracellular signaling interactions that may evolve during treatment and contribute to therapeutic resistance [13]. These observations suggest that future diagnostic strategies should combine conventional histological grading and staging with selected microenvironmental biomarkers. Nevertheless, clinical implementation should be based on validated indications, because many potentially relevant morphological and molecular features remain investigational. The presence of an association between a microenvironmental characteristic and treatment response does not independently establish that modifying that feature will improve patient survival.

DISCUSSION

The present review demonstrates that histopathological characteristics of the tumor microenvironment provide important information about malignant progression beyond the conventional morphological evaluation of neoplastic cells. Although tumor-cell atypia, differentiation, mitotic activity, and invasion remain fundamental diagnostic parameters, the biological behavior of malignant neoplasms also reflects interactions with immune cells, fibroblasts, extracellular matrix structures, and vascular components. These interactions contribute to the development of invasive growth patterns, immune evasion, altered metabolism, and treatment resistance. One of the most important findings of contemporary research concerns the prognostic relevance of immune-cell localization. The investigations conducted by Galon and colleagues and the subsequent international validation of the Immunoscore demonstrated that the density and anatomical distribution of selected T lymphocyte populations may provide clinically relevant prognostic information in colorectal cancer. Similar findings in breast cancer suggest that stromal lymphocytic infiltration can be associated with response to neoadjuvant therapy, particularly in selected molecular subtypes. However, the prognostic significance of immune infiltration is not uniform across all malignancies, and its interpretation depends on tumor biology, immune-cell phenotype, and the methodology used for assessment. The importance of standardized evaluation is therefore considerable. The recommendations developed by Salgado and colleagues for tumor-infiltrating lymphocytes and the international consensus regarding tumor budding illustrate how morphological observations can be transformed into more reproducible diagnostic parameters. Nevertheless, standardization does not eliminate biological heterogeneity, and the clinical value of any histopathological marker must be established within the specific tumor type and patient population in which it is intended to be used.

The structural characteristics of tumor-associated stroma represent another important aspect of malignant progression. Fibroblast activation and extracellular matrix remodeling may influence cellular

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migration, tissue stiffness, metabolic conditions, and immune-cell distribution. However, the functional diversity of cancer-associated fibroblasts demonstrates that the relationship between stromal density and cancer aggressiveness is not necessarily linear. Some fibroblast populations may contribute to tumor progression through matrix remodeling and immunosuppressive signaling, whereas others may retain protective functions or restrict malignant growth under particular conditions. Consequently, therapeutic strategies aimed at indiscriminate destruction of stromal tissue may not produce favorable outcomes in all cancers. Similar complexity is observed in tumor-associated angiogenesis, where abnormal vascular structures may impair perfusion and drug delivery, while certain interventions may temporarily improve vascular function through normalization. The histopathological analysis of these processes requires integration of structural observations with the biological mechanisms responsible for their development. Desmoplastic reactions, vascular abnormalities, stromal inflammatory infiltration, and invasive margins provide useful morphological information, but they should not automatically be interpreted as specific molecular phenomena without additional evidence. For example, increased stromal fibrosis does not independently establish the presence of a particular fibroblast phenotype, while morphological evidence of necrosis does not precisely quantify tumor hypoxia. Similarly, immunohistochemical markers may identify broad cell populations but do not always establish their functional characteristics. The integration of morphology with validated immunohistochemical and molecular techniques may therefore improve pathological interpretation while reducing the risk of overly simplified biological conclusions.

Recent developments in spatial transcriptomics and artificial intelligence demonstrate the potential for more comprehensive characterization of tumor ecosystems. The 2026 studies by Li and colleagues provide evidence that spatial relationships between malignant, stromal, and immune cells contain clinically relevant information that may be difficult to detect through conventional examination alone. The identification of recurrent cellular niches across different cancer types suggests that certain organizational principles may be shared among malignant tissues, although the biological meaning of individual niches depends on their cellular composition and anatomical context. The development of AI-assisted prediction from conventional histological slides may increase access to spatial information by using routinely available pathological material. However, algorithms trained on selected datasets may perform differently when applied to new patient populations, tissue preparation protocols, staining procedures, or imaging equipment. Furthermore, spatial prediction does not necessarily replace direct molecular measurement, and computationally inferred cellular identities may be affected by uncertainty when different cell types share similar morphological features. The clinical integration of such technologies therefore requires transparent validation procedures, assessment of interlaboratory reproducibility, and demonstration of benefits for patient management. For pathological anatomy research in Uzbekistan, prospective or retrospective investigations involving archived histological preparations could examine the relationships between stromal lymphocytic infiltration, tumor budding, vascular density, and established clinicopathological characteristics. However, appropriate

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methodology would require standardized tissue selection, validated scoring systems, clearly defined clinical outcomes, and accurate documentation of patient characteristics. Future local studies could also evaluate the reproducibility of digital pathology methods and the feasibility of integrating immunohistochemical markers with routine morphological assessment. The present review is limited by its narrative design, differences among the analyzed cancer types, and the predominance of observational evidence concerning several microenvironmental mechanisms. Despite these limitations, the available scientific literature supports the growing importance of tumor microenvironment analysis in contemporary histopathology and precision oncology.

CONCLUSION

The tumor microenvironment is a complex and dynamic biological system whose structural and functional characteristics contribute substantially to cancer progression, local invasion, metastatic dissemination, and therapeutic resistance. Histopathological features such as tumor-infiltrating lymphocytes, cancer-associated fibroblasts, desmoplastic stromal reactions, extracellular matrix remodeling, abnormal vascular structures, and tumor budding reflect important interactions between malignant cells and surrounding tissues. The density, functional characteristics, and spatial distribution of immune-cell populations may provide clinically relevant prognostic information, while stromal architecture and invasive growth patterns contribute to the morphological assessment of tumor aggressiveness. International investigations involving colorectal and breast cancer demonstrate that selected microenvironmental parameters can complement conventional pathological staging and improve understanding of therapeutic responsiveness. Recent advances in spatial transcriptomics and AI-assisted digital pathology have further expanded the possibilities for characterizing tumor ecosystems and identifying biologically relevant cellular neighborhoods. Nevertheless, microenvironmental heterogeneity, differences between cancer types, and limitations of current diagnostic methods require careful interpretation of these findings. Future investigations should prioritize standardized morphological assessment, validation of spatial biomarkers, integration of histopathology with molecular technologies, and prospective evaluation of their clinical significance. A comprehensive understanding of the tumor microenvironment may contribute to more accurate prognostic stratification, improved therapeutic decision-making, and further development of personalized oncology.

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