Zabrodskyi Ihor Serhiiovych, 3rd year student of medical faculty of Bukovinian State Medical University, Chernivtsi, Ukraine, https://orcid.org/0009-0005-3576-6828

Pankiv Tetiana Vasylivna, PhD, Assistant Professor of Department of Pathological Anatomy, Bukovinian State Medical University, Chernivtsi, Ukraine, https://orcid.org/0000-0002-2525-562X

Khmara Tatiana Volodymyrivna, Doctor of Medicine Sciences, Professor, Professor of the Department of Human Anatomy named after MG Turkevich of the Bukovinian State Medical University, Chernivtsi, https://orcid.org/0000-0003-4699-6600

ANGIOGENESIS AS A MORPHOLOGICAL MARKER OF TUMOR GROWTH: AN ANALYSIS OF CURRENT LITERATURE DATA

Abstract

Introduction. The issue of tumor growth remains one of the most pressing challenges in contemporary biomedical science due to the high prevalence of oncological diseases and the complexity of their pathogenesis. Angiogenesis ensures tumor vascularization, oxygen and nutrient supply, and contributes to invasion and metastasis, while its morphological manifestations are used to assess tumor progression and prognosis.

The aim of study was to analyze and summarize current literature data on angiogenesis as a morphological marker of tumor growth.

Results. Analysis of recent publications shows that tumor angiogenesis occurs through classical formation of new blood vessels (sprouting) as well as alternative mechanisms such as vessel co-option and vasculogenesis. VEGF plays a central role, with its activity correlating with increased microvascular density and poor prognosis. Perivascular spaces, cells of the tumor microenvironment, and

tumor-associated macrophages play important regulatory roles, stimulating the formation of pathological vascular networks and increasing tumor invasiveness. Metabolic and epigenetic mechanisms (e.g., m6A RNA modifications) additionally influence the intensity of angiogenesis, as well as the structure and architecture of the tumor vascular network, allowing assessment of its growth dynamics, degree of aggressiveness, and morphological changes.

Conclusions. Angiogenesis is a universal and multifaceted morphological marker of tumor growth, reflecting the integration of molecular, cellular, and tissue-level processes. Further research should focus on understanding these mechanisms in greater detail to improve tumor characterization and prognostic assessment.

Keywords: angiogenesis, tumor growth, vascular endothelial growth factor (VEGF), tumor, pathomorphology.

Problem Statement. Tumor growth remains one of the most pressing issues in modern biomedical science due to the high prevalence of oncological diseases, the complexity of their pathogenesis, and significant mortality rates. According to the World Health Organization, nearly ten million people died from cancer in 2020, meaning that approximately one in six deaths worldwide is attributable to this disease [1]. Similarly, Ukraine demonstrates high mortality rates, with about 85,000 deaths from cancer reported annually [2].

Over recent decades, tumor growth has increasingly attracted scientific attention, as its development is a multifactorial process involving disturbances in cellular proliferation, differentiation, apoptosis, and intercellular interactions.

One of the key mechanisms underlying the progression of malignant neoplasms is angiogenesis—the process of new blood vessel formation from the pre-existing vasculature. Activation of angiogenesis creates conditions that supply tumor tissue with oxygen and nutrients, promotes invasive growth, and facilitates

metastasis. In this regard, angiogenesis is considered not only a prerequisite for tumor growth but also an important morphological marker of malignant tissue transformation that warrants thorough investigation.

In light of the above, the analysis of current literature data on angiogenesis as a morphological marker of tumor growth is justified from the perspective of the need to systematize existing scientific evidence.

Analysis of Recent Research and Publications. In recent years, angiogenesis has remained one of the most relevant research areas in oncology due to its pivotal role in tumor vascularization, growth, and metastasis. Contemporary reviews and studies emphasize the complex nature of angiogenesis, which involves multiple mechanisms of new vessel formation, including sprouting angiogenesis, vessel co-option, vasculogenesis, and other pathways independent of vascular endothelial growth factor (VEGF – vascular endothelial growth factor). These alternative mechanisms may contribute to the development of resistance to anti-angiogenic therapies. Such a broad classification of angiogenic mechanisms expands the understanding of their impact on tumor development and prognosis [3–5].

Individual studies focused on specific tumor localizations, particularly breast cancer, confirm the high prognostic value of microvessel density and the expression of angiogenic factors in assessing tumor aggressiveness and disease outcomes. It has been established that poor prognosis in breast cancer correlates with increased microvessel density and enhanced activity of pro-angiogenic factors, which supply tumor tissue with oxygen and nutrients. Inhibition of angiogenesis leads to reduced tumor vascularization and restriction of its metabolic support; therefore, tumor angiogenesis is considered an important therapeutic target [6].

Overall, current reviews confirm that angiogenesis is not only a key mechanism of tumor growth but also a significant indicator for prognosis, assessment of therapeutic response, and the development of novel multitarget

treatment strategies in oncology. Accordingly, systematization of contemporary literature data on angiogenesis and its stimulating factors is warranted [7].

The aim of study was to analyze and summarize current literature data on angiogenesis as a morphological marker of tumor growth.

Materials and Methods. A total of 87 recent scientific publications published between 2020 and 2025 were reviewed. The sources were retrieved from the PubMed, Scopus, Web of Science, and Google Scholar databases. Based on their relevance to the study objective, methodological rigor, and scientific significance, 20 publications were selected for inclusion in the final version of the article.

Presentation of the Main Material. The conducted analysis of contemporary literature sources indicates that angiogenesis is one of the key biological processes determining the growth, progression, and metastatic potential of malignant tumors. The formation of new blood vessels supplies tumor tissue with oxygen and nutrients, thereby creating the morphological basis for the transition from non-invasive (initial) growth to invasive progression [8]. From this perspective, angiogenesis is considered not only a functional mechanism but also an important morphological marker of tumor growth with diagnostic and prognostic significance.

Contemporary studies confirm that the activation of angiogenesis in tumors is driven by a complex interplay between hypoxia, cellular metabolic reprogramming, and signals derived from the tumor microenvironment. A central role in this process is played by vascular endothelial growth factor (VEGF), the expression of which is significantly upregulated under hypoxic conditions and correlates with increased microvessel density and poor prognosis. According to a study published in *Oncology Letters* (Zhou J., 2024), VEGF-dependent signaling cascades contribute to the formation of a morphologically immature and

chaotically organized vascular network characteristic of tumor tissue, thereby promoting invasion and metastasis [9].

An important addition to the classical concepts of angiogenesis is the growing evidence regarding the role of epigenetic mechanisms, particularly N6-methyladenosine (m6A) RNA modification. A study by Qin L. (2024), published in *Frontiers in Oncology*, demonstrates that m6A regulators influence the stability and translation of mRNAs encoding key pro-angiogenic factors, including VEGF, FGF, and angiopoietins. Disruption of m6A balance leads to enhanced angiogenesis and the development of an aggressive tumor phenotype [10].

The metabolic aspects of angiogenesis have also attracted considerable attention. In a publication by Arce-Recatala C. (2025) in *Metabolites*, it is emphasized that tumor cells and endothelial cells exist in close metabolic symbiosis. Reprogramming of glycolysis, lipid metabolism, and amino acid metabolism promotes activation of angiogenic signaling pathways and is reflected in characteristic morphological alterations of the tumor vasculature. Thus, the metabolic profile of a tumor is directly associated with the degree of angiogenesis and may be considered as its functional and morphological correlate [11].

The immune microenvironment also plays a distinct role in the regulation of tumor angiogenesis. According to Qiao X. (2025) in *Frontiers in Immunology*, tumor-associated macrophages (TAMs) represent one of the key sources of pro-angiogenic factors. They stimulate endothelial cell proliferation, extracellular matrix (ECM) remodeling, and the formation of a pathological vascular network. Morphologically, this is manifested by increased microvessel density and structural atypia, which are associated with an immunosuppressive microenvironment and tumor progression [12].

Perivascular spaces, particularly the Virchow–Robin spaces, play a significant role in tumor angiogenesis and microenvironmental cell interactions. In the context of tumors of the nervous system, these structures constitute an

important microanatomical component of the vascular microenvironment, facilitating the diffusion of oxygen, nutrients, and signaling molecules, as well as the migration of immune and tumor cells [13]. In malignant brain tumors, such as high-grade gliomas, these spaces are regarded not merely as anatomical formations but also as functional pathways of interaction between tumor cells, the vascular wall, and microenvironmental cells [14]. Available data indicate that tumor cells are capable of exploiting perivascular spaces for migration along the vascular network, a phenomenon closely associated with pathological angiogenesis and invasive growth [15].

Activation of angiogenesis in brain tumors is accompanied by the formation of a morphologically immature and structurally atypical vascular network, around which remodeling and dilation of perivascular spaces are observed. This creates conditions for the accumulation of pro-angiogenic factors, immune microenvironment cells, and tumor cells, thereby enhancing the invasive potential of the neoplasm [16]. Accordingly, Virchow–Robin spaces may be considered as a morphological indicator of active vascular remodeling and angiogenesis in brain tumor tissue.

Contemporary concepts of tumor angiogenesis extend beyond the classical formation of new blood vessels and include alternative mechanisms of vascular network development. One such mechanism is vessel co-option, whereby cancer cells do not generate new vessels but instead use pre-existing capillaries of healthy tissue, adapting them to tumor needs. Another important process is vasculogenesis, in which new vessels arise not through sprouting of existed ones but via differentiation of endothelial or stem cells into vascular endothelium. These alternative pathways ensure tumor blood supply even when classical angiogenesis is suppressed or insufficient and contribute to increased invasiveness and resistance to anti-angiogenic therapies [4, 17].

The integration of morphological and mathematical approaches enables a deeper understanding of tumor angiogenesis patterns. In a study by Mohseni A. (2024), published in *Frontiers in Biomedical Technologies*, the potential of mathematical modeling of angiogenesis was demonstrated for quantitative assessment of vascular architectonics and prediction of tumor growth. Such models highlight the close relationship between vascular morphology and the functional behavior of tumors [18].

Several review papers also emphasize the importance of an interdisciplinary approach to angiogenesis research, combining molecular, morphological, and clinical data. In particular, analyses of current concepts of angiogenesis as a biomarker and therapeutic target confirm its pivotal role in patient stratification and prognosis assessment [19, 20].

Conclusions and Prospects for Further Research. Thus, angiogenesis represents a universal yet multifaceted morphological marker of tumor growth. Its manifestations reflect the integration of hypoxic, metabolic, epigenetic, and immune mechanisms that shape the structural and functional basis of malignant tumor progression.

Future research should focus on the development of individualized therapeutic approaches that take into account the molecular profile of the tumor and the status of angiogenesis. An important direction is also the combination of conventional anticancer treatment modalities with targeted anti-angiogenic inhibitors, which may enhance therapeutic efficacy and reduce the risk of complications.

References

1. World Health Organization. (2025). *Cancer*. https://www.who.int/news-room/fact-sheets/detail/cancer

2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today

3. Zhang, R., Yao, Y., Gao, H., & Hu, X. (2024). Mechanisms of angiogenesis in tumour. *Frontiers in Oncology*, *14*, 1359069. Available from: https://doi.org/10.3389/fonc.2024.1359069

4. Ribatti, D., Annese, T., & Tamma, R. (2023). Vascular co-option in resistance to anti-angiogenic therapy. *Frontiers in oncology*, *13*, 1323350. Available from: https://doi.org/10.3389/fonc.2023.1323350

5. Belotti, D., Pinessi, D., & Taraboletti, G. (2021). Alternative Vascularization Mechanisms in Tumor Resistance to Therapy. *Cancers*, *13*(8), 1912. Available from: https://doi.org/10.3390/cancers13081912

6. Gamde, S. M., & Ogenyi, O. D. (2024). Angiogenesis in breast cancer: A review. Asian Pac J Cancer Biol, 9 (1), 97-103. Available from: https://doi.org/10.31557/apjcb.2024.9.1.97-103

7. Liu, Z. L., Chen, H. H., Zheng, L. L., Sun, L. P., & Shi, L. (2023). Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal transduction and targeted therapy*, *8*(1), 198. Available from: https://doi.org/10.1038/s41392-023-01460-1

8. Liu, X., Zhang, J., Yi, T., Li, H., Tang, X., Liu, D., ... & Li, Y. (2025). Decoding tumor angiogenesis: pathways, mechanisms, and future directions in anti-cancer strategies. *Biomarker Research*, *13*(1), 62. Available from: https://doi.org/10.1186/s40364-025-00779-x

9. Zhou, J., Zhou, P., Wang, J., & Song, J. (2024). Roles of endothelial cell specific molecule1 in tumor angiogenesis. *Oncology Letters*, *27*(3), 137. Available from: https://doi.org/10.3892/ol.2024.14270

10. Qin, L., Zeng, X., Qiu, X., Chen, X., & Liu, S. (2024). The role of N6-methyladenosine modification in tumor angiogenesis. *Frontiers in Oncology*, *14*, 1467850. Available from: https://doi.org/10.3389/fonc.2024.1467850

11. Arce-Recatala, C., & Oberkersch, R. E. (2025). Endothelial Arginine Metabolism in Angiogenesis: Mechanistic Insights from Tissue Repair to Tumor Progression. *Metabolites*, *15*(11), 694. Available from: https://doi.org/10.3390/metabo15110694

12. Qiao, X., Song, Z., Geng, L., Xing, L., & Wang, Y. (2025). Investigating the role of tumor cell heterogeneity and angiogenesis genes in the prognosis of multiple myeloma. *Frontiers in Immunology*, *16*, 1610833. Available from: https://doi.org/10.3389/fimmu.2025.1610833

13. Zabrodskyi I. S., Protsak T. V. Rol peryvaskuliarnykh prostoriv (prostory Virkhova—Robina) u rehuliatsii anhiogenezu v mozku. Mizhdystsyplinarni naukovi doslidzhennia ta perspektyvy yikh rozvytku: materialy VIII Mizhnarodnoi studentskoi naukovoi konferentsii, m. Ivano-Frankivsk, 30 sichnia, 2026 rik / HO «Molodizhna naukova liha». — Vinnytsia: TOV «UKRLOGOS Hrup», 2026. S. 242–244.

14. Demir, E., Montgomery, D., Saloum, A., Yaghi, N., & Karsy, M. (2025). Current Understanding Regarding the Glioma Microenvironment and Impact of the Immune System. *Neuroglia*, *6*(1), 13. https://doi.org/10.3390/neuroglia6010013

15. Ravin, R., Suarez-Meade, P., Busse, B., Blank, P. S., Vivas-Buitrago, T., Norton, E. S., ... & Quiñones-Hinojosa, A. (2023). Perivascular invasion of primary human glioblastoma cells in organotypic human brain slices: human cells migrating in human brain. *Journal of neuro-oncology*, *164*(1), 43-54. https://doi.org/10.1007/s11060-023-04349-9

16. Mosteiro, A., Pedrosa, L., Ferrés, A., Diao, D., Sierra, À., & González, J. J. (2022). The Vascular Microenvironment in Glioblastoma: A Comprehensive Review. *Biomedicines*, *10*(6), 1285. https://doi.org/10.3390/biomedicines10061285

17. Zhang, R., Yao, Y., Gao, H., & Hu, X. (2024). Mechanisms of angiogenesis in tumour. *Frontiers in Oncology*, *14*, 1359069. https://doi.org/10.3389/fonc.2024.1359069

18. Mohseni, A., Pooyan, M., Raiesdana, S., & Menhaj, M. B. (2024). The Effect of Tumor Angiogenesis Agents on Tumor Growth Dynamics: A Mathematical Model. *Frontiers in Biomedical Technologies*. Available from: https://doi.org/10.18502/fbt.v12i1.17743

19. Venketesh K. Panda and Sumant K. Mohanty (2025) Deciphering the Role of Tumor-Associated Macrophages (Tams) in Tumor Angiogenesis. J of Clin Onco & Adv Thpy 1(2), 01-08. Available from: https://doi.org/10.63721/25JCOAT0104

20. Pang, L., Liu, S., Liu, C., Hu, S., Zhang, Z., & Tian, T. (2025). Dynamic modeling and analysis of tumor angiogenesis and anti-angiogenesis treatment. *Journal of Biological Systems*, *33*(02), 647-667. Available from: https://doi.org/10.1142/S0218339025500172