The Role of Microvascular Density (MVD) in Cervical Cancer: A Article Review

I Gede Sastra Winata, Made Bagus Dwi Aryana, Kadek Fajar Marta, Fenyta Christyani
Obstetrics and Gynecology Department RSUP Prof Dr. IGNG Ngoerah Denpasar, Bali, Indonesia
Correspondence: I Gede Sastra Winata, Email: sastrawinatastw@gmail.com

Abstract
Introduction: The development, invasion and metastasis process of cervical cancer is closely related to the ability of cancer cells in the process of tumor oxygenation and the process of angiogenesis. Angiogenesis plays a very important role in the growth, metastasis and progression of tumor cells. Microvascular Density (MVD) is an examination that counts the number of microvasculature compared to the area of tissue analyzed by histology and immunohistochemistry.
Method: This study reviewed literature by searching the Pubmed, ScienceDirect, and Cochran Library Database. The search query included "microvascular" and "cervical cancer". The study was reviewed using the Preferred Reporting Item for Systemic Reviews and Meta-Analyses (PRISMA) standards. The scope of analysis was restricted to clinical trials conducted from 2011 to 2023
Result: Currently, MVD examination is an examination that is often carried out to evaluate the process of intratumor angiogenesis in cancer. By knowing the MVD value in cancer sufferers, it is hoped that it can be considered in determining therapy and assessing the outcome of the course of cervical cancer which can be considered as a prognostic factor. Apart from that, it can complement the theory of other biomolecular prognostic factors that play a role in cervical cancer such as vascular endothelial growth factor (VEGF), Ki-67 protein, p53 tumor suppressor gene, oxygenation factors, especially hypoxia inducible factors-1α (HIF-1α), enzymes protease (matrix metalloproteinase), and cell adhesion molecules (E-Kadherin, catenin).
Conclusion: The role of MVD in cervical cancer sufferers as an indicator of prognosis and success of therapy.

Keywords : Cervical Cancer, Diagnosis, Microvascular Density

Peranan Kepadatan Mikrovaskuler (MVD) pada Kanker Serviks: Sebuah Ulasan Artikel

Abstrak
Pendahuluan : Proses perkembangan, invasi dan metastasis kanker serviks erat kaitannya dengan kemampuan sel kanker dalam proses oksigenasi tumor dan proses angiogenesis. Angiogenesis memainkan peran yang sangat penting dalam pertumbuhan, metastasis, dan perkembangan sel tumor. Kepadatan Mikrovaskular (MVD) merupakan pemeriksaan yang menghitung jumlah mikrovaskular dibandingkan dengan luas jaringan yang dianalisis secara histologi dan imunohistokimia.
Metode: Pencarian literatur dilakukan pada database PubMed dan ScienceDirect dan Cochrane Library. Pencarian dilakukan menggunakan istilah "mikrovaskular" dan "kanker serviks". Penulisan sistematik review disesuaikan dengan pedoman *Professed Reporting for Systematic Review and Meta-Analysis* (PRISMA). Semua studi yang diinklusi merupakan uji klinis pada periode tahun 2011 – 2023.
Hasil: Saat ini MVD merupakan pemeriksaan yang sering dilakukan untuk mengevaluasi proses angiogenesis intratumor pada kanker. Dengan mengetahui nilai MVD pada penderita kanker diharapkan dapat menjadi pertimbangan dalam menentukan terapi dan menilai luaran perjalanan penyakit kanker serviks yang dapat diperhitungkan sebagai faktor prognosis. Selain itu dapat melengkapi teori faktor prognostik biomolekuler lain yang berperan dalam kanker serviks seperti faktor pertumbuhan endotel vaskular (VEGF), protein Ki-67, gen penekan tumor p53, faktor oksigenasi, terutama faktor pemicu hipoksia-1 α (HIF-1 α), enzim protease (matrix metalloproteinase), dan molekul adhesi sel (E-Kadherin, catenin).
Kesimpulan: MVD pada penderita kanker serviks berperan sebagai indikator prognosis dan keberhasilan terapi

Kata kunci: Kanker Serviks, Diagnosis, Kepadatan Vaskular

Introduction

In recent times, the handling of cervical cancer cases has progressed both in terms of prevention, early detection and treatment. Various government policies have been implemented to reduce the prevalence of cervical cancer.

Cervical cancer is the most common cancer in four people globally with an estimated 604,000 new cases with a death toll of 342,000 in 2020.[1] 90% of new cases come from developing countries with low to lower middle socioeconomic levels. This is a challenge for the World Health Organization (WHO) to eradicate cervical cancer cases through comprehensive treatment through primary prevention through Human Papilloma Virus (HPV) vaccination, secondary prevention (screening and therapy of pre-cancer cases), tertiary prevention (diagnosis and case management). and palliative care. Two types of HPV, namely types 16 and 18, play a role in more than 50% of cervical cancer cases.[2] WHO created a commemorative program on February 4 with the slogan of eliminating chaos in the handling of cancer cases in various countries. For cervical cancer cases, various programs are being promoted, namely HPV vaccination with a target of more than 90%, early detection with various screening examinations such as pap smears, HBV DNA testing with a target of more than 70% and handling of cervical cancer cases.[3]

The high number of cervical cancer cases has encouraged the development of knowledge related to things that influence the process of tumor replication, invasiveness and metastasis.[4] The development, invasiveness and metastatic process of cervical cancer is closely related to the ability of cancer cells in the process of tumor oxygenation and the process of angiogenesis. Angiogenesis plays a very important role in the growth, metastasis and progression of tumor cells. When the tumor size reaches more than 1 mm, an angiogenesis process occurs which will further trigger tumor metastasis.[5]

There are several biomarkers that can detect angiogenesis, including Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF) and Microvascular Density (MVD).[6,7]

Microvascular Density is an examination that counts the number of microvasculature compared to the area of a tissue analyzed by histology and immunohistochemistry.[8] Currently, MVD is an examination that is often carried out to monitor the process of intratumor angiogenesis in cancer. In the early 1990s, MVD was first introduced as an indicator for assessing the outcome of a cancer which was first studied in breast cancer.[9] Several antibodies that are often used in microvascular staining are CD31, CD34, CD105 (Endoglin) and anti-factor VIII (Von Willebrand Factor).[10]

By knowing the MVD value in cancer sufferers, it is hoped that it can be considered in determining therapy and assessing the outcome of the course of cervical cancer which can be taken into account as a prognostic factor. Although several clinicopathological factors such as age, parity, Body Mass Index (BMI), lesion stage, lesion size, histology, degree of differentiation, lymphatic and vascular invasion, and lymph node metastasis also determine the outcome of cervical cancer.[11]

Based on the explanation above, it is important to know MVD in cervical cancer sufferers as an indicator of prognosis and success of therapy. Apart from that, it can complement the theory of other biomolecular prognostic factors that play a role in cervical cancer such as vascular endothelial growth factor (VEGF), Ki-67 protein, p53 tumor suppressor gene, oxygenation factors, especially hypoxia inducible factor-1α (HIF-1α), protease enzymes (matrix metalloproteinase), and cell adhesion

molecules (E-Kadherin, catenin).[11,12]

Discussion

Cervical cancer is a cancer that is often found in women and is ranked the fourth most common cancer in the world after breast, colorectal and lung cancer. Several things that are considered risk factors for cervical cancer are predisposing factors for exposure to HPV, namely early age at first sexual intercourse, giving birth to children at an early age, changing sexual partners), low socioeconomic status, smoking, immunodeficiency (HIV infection), and immunosuppression (autoimmune disorders, solid organ transplant recipients, administration of chemotherapy, and chronic use of steroids).[13]

Most women with cervical cancer can have normal general physical examination findings, especially in the early stages of the disease. As the disease progresses, hydronephrosis indicates ureteral obstruction. In these cases, Costovertebral angle (CVA) tapping pain may be found. A speculum examination (Inspekulo) of the cervix may look normal if the cancer is still microinvasive. Visible cervical cancer lesions display varying appearances. Lesions can be exophytic or endophytic growths; polypoid mass, papillary tissue, or barrel-shaped cervix; cervical ulceration or granular mass; or necrotic tissue. Watery, purulent, or bloody discharge may also be visible. In cases of advanced cervical cancer, the lesion can spread to the vagina and the spread of the disease can be determined during palpation of the vaginal walls. A clinician can palpate an enlarged uterus due to tumor invasion and growth. The presence of hematometra or pyometra can also widen the endometrial cavity after obstruction of the fluid outlet by cervical cancer. In this case, the size of the uterus may feel enlarged[13–15].

Angiogenesis is an important step for tumor growth and plays an important role in cancer metastasis.[16] Angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and host cells near the tumor.[17] Angiogenesis occurs throughout life. There is no tissue in the body that does not go through the process of angiogenesis. Changes in metabolic activity lead to proportional changes in angiogenesis and in capillarity. Oxygen plays an important role in this regulation. Hemodynamic factors are essential for the survival of vascular tissue and for the structural adaptation of the vascular wall.[18]

Tumor angiogenesis is an important process by which tumor cells can grow, invade, and metastasize. Tumor angiogenesis is positively correlated with tumor malignancy. Angiogenic factors, cytokines, and free non-coding RNAs in the tumor microenvironment can promote tumor angiogenesis. It is these angiogenic factors that play an important role in regulating normal and abnormal angiogenesis. There are 3 types of peptides that are important for regulating angiogenesis, including VEGF, FGF, and platelet-derived growth factor (PDGF).[19]

The tumor microenvironment itself is formed by a combination of tumor cells and stroma, the Extracellular Matrix (ECM), and secreted factors, so it fits perfectly into the definition of an ecosystem. Changes in tumor cell gene expression trigger disruption of normal tissue homeostasis, favoring the secretion of certain molecules (cytokines, growth factors, etc.) that recruit stromal cells. The cells that make up the tumor stroma itself are Cancer-associated Fibroblasts (CAF), endothelial cells, pericytes, adipocytes, and immune cells, including monocytes, macrophages, lymphocytes, and dendritic cells. These cells are enclosed in a heterogeneously deposited ECM and are influenced by changes in biophysical parameters including oxygenation and pH.[20]

This angiogenesis process is activated in response to hypoxia, which, together with the presence of nutritional deprivation conditions, can amplify the expression of inflammatory signals and cytokines that recruit vascular cells for tumor vascular plexus formation. Early in tumor development, hypoxia triggers the transcription of several genes that are key mediators of the angiogenic process, such as VEGF and PDGF. Mechanistically, activation of angiogenic processes involves breakdown of the vascular ECM at different rates for subsequent endothelial cell invasion and tube formation. Apart from the role of tumor cells as the main secretors of endothelial cell promoters, interactions with other stromal cells such as pericytes are also required for neovessel stability.[11]

In addition to playing a role in the maintenance of the primary tumor ecosystem, tumor angiogenesis enables the invasion and dissemination of tumor cells and supports the creation of a new secondary tumor ecosystem at the site of metastasis. VEGF-mediated stimulation of blood and lymphatic endothelial cells provides a large vascular area for tumor cell intravasation, in addition to increasing vascular permeability. In tumor endothelial cells, VEGF increases protease secretion, contributes to basement membrane degradation, and increases the expression of molecules that mediate tumor-endothelial cell interactions. When tumor expansion occurs, the inner tumor cells move away from the blood supply site and become relatively hypoxic. Hypoxia increases the expression of many angiogenic growth factors in tumor cells.

Tumor growth and metastasis rely on angiogenesis, and inhibition of angiogenesis can be used as a therapeutic strategy for tumor treatment. Recently, targeting pro-angiogenic genes has become a research hotspot for tumor therapy and prevention of tumor expansion. Currently FDA-approved anti-angiogenic drugs are categorized into two types based on the number of targets: single-target inhibitors and multi-target inhibitors. Angiogenesis inhibitors have been divided into two main classes depending on their mode of action and target cells. Direct angiogenesis inhibitors act directly on Endothelial Cells (ECs), but may also have off-target effects on tumor cells. Direct angiogenesis inhibitors usually block EC proliferation or motility regardless of the stimulator. Its mode of action may be downstream of growth factor-induced signal transduction cascades, therefore incubation of ECs with these direct inhibitors defeats the action of growth factors such as VEGF or FGF.[12]

On the other hand, angiogenesis inhibitors do not directly block growth factors or cell pathways other than ECs. Examples of indirect inhibitors include antibodies to growth factors such as anti-VEGF, soluble receptors of the VEGF receptor, or pericyte recruitment inhibitors. Because angiogenesis inhibitors do not directly block tumor cell-derived factors, they tend to produce resistant tumors that produce alternative angiogenic factors.[13]

The main effects of angiogenic inhibitors can be classified according to their effect on: inhibition, regression, or normalization of tumor vasculature. Because of the complexity of tumor angiogenesis, direct inhibition of vascular signaling includes inhibitors of VEGF ligands, inhibitors of VEGFR receptors, and inhibitors of other growth factors released by stromal or tumor cells. Another example is Tyrosine Kinase (TK) inhibitors, which block activation of endothelial cells and pericytes, thereby inhibiting proliferation, migration, and survival. Novel antiangiogenic strategies are directed towards inhibition of Endothelial Progenitor Cell (EPC) recruitment, via stromal-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) signaling, and inhibition of extracellular matrix (ECM) remodeling.[14]

Microvessel density (MVD) calculation

is one of the most representative methods for measuring angiogenesis of cancer tissue in humans.[14] This method requires vascular endothelium markers to visualize microvessels detected by immunohistochemistry (IHC).[15] Microvascular density (MVD) is an examination that measures the number of blood vessels, which is calculated based on per unit area or per field of view. [16] MVD can be considered as a quantitative calculation of blood vessels that reflects the process of angiogenesis.[17]

The counting mechanism or procedure relies on the observer's assessment of the blood vessels. This assessment may be difficult in areas where the observed vessels appear tortuous and have been cut several times, where they may be counted as one or possibly several microvessels, depending on the observer's assessment.[18]

Different methods based on computerized image analysis have been developed to measure immunohistochemical staining, and have therefore been proposed to eliminate subjective differences in microvessels.[29] These computer systems have their own general and specific problems, in addition to capital and operational costs. Measurement of the endothelial area according to the surface of the endothelial structure being stained, the microvessel perimeter and the microvascular area consisting of the endothelial area plus the lumen of the blood vessel, has been used as a more accurate index of tumor vascularization.[18,20]

The total microvascular area (TVA) is occupied by microvessels per unit area of the tumor in a limited number of fields (three or four), selected subjectively from the most vascularized areas (hot spots). The branch count is the number of blood vessel branches per 100 blood vessel sections. There is usually a positive correlation between MVD and number of branches.[12]

MVD was calculated as the arithmetic mean of the number of microvessels from three fields of view with the greatest vascularity located on two different casts from the same patient. Under 100× magnification, the location with the greatest vascularization (hotspot) was selected, and individual microvessels were counted under 400× magnification. Each immunopositive structure (round, oval, and irregular) separated from other profiles or tissue elements was counted as one blood vessel. Each colored cell or group of cells was considered a blood vessel regardless of the presence of a blood vessel lumen. Vessels with visible muscle layers and visible morphotic elements in the lumen were not counted as microvessels. The final result is expressed as the number of blood vessels in the field of view with a magnification of 400x..[13]

Tumors are thought to secrete angiogenic factors that promote neovascularization around them. Several factors have been identified, including vascular endothelial growth factor (VEGF) and Platelet-derived Endothelial Cell Growth Factor (PD-ECGF) which have angiogenic activity in vivo[14]. Angiogenesis is a stage in tumorigenesis that causes treatment failure in patients with cancer.

The development of carcinoma is associated with two phases of tumor growth. First, the "prevascular phase" in which tumor growth is very limited to only 2 or 3 mm in size, can persist for years, and is incapable of metastasizing, as demonstrated in cervical cancer by Sillman in 1981. In contrast, the ''vascular phase'' ' which is the second phase characterized by rapid tumor growth and metastatic potential. Tumor cells must gain access to the vasculature in the primary tumor, survive in the circulation, stall in the microvasculature, grow in target organs, and induce angiogenesis. The formation of this microvasculature is a local response of the host to the metabolic needs of a proliferating tumor, mediated by complex biomolecular mechanisms, allowing tumor cells to grow and

providing entry into the systemic circulation. It is clear that tumors rarely spread in the pre-vascular phase of the disease.[13]

Cancer cells that escape into the tumor's blood vessel tissue can begin the process of angiogenesis which allows the expansion of the tumor mass. The TGF-β signaling pathway is also involved in endothelial cell differentiation and plays an important role in angiogenesis. Unlike these angiogenesis molecules, endoglin (ENG) binds to TGF-β1 and -β3, interacting with TGF-β type I and II receptor signaling complexes. In humans, Hereditary Haemorrhagic Telangiectasia type 1 (HHT1), characterized by vascular malformations, is associated with ENG gene mutations. Therefore, MVD assessed by ENG has been correlated with malignant tumor angiogenesis.[15]

There are various biomarkers to measure intratumoral angiogenesis, including vascular endothelial growth factor (VEGF), growth factor bFGF and microvessel density (MVD). The most commonly used antibodies for microvessel staining are CD31, CD34, CD105 (Endoglin) and anti-factor VIII (Von Willebrand Factor).[16] Several studies have shown that MVD expression is significantly associated with poor overall survival. Numerous studies have shown that MVD plays a potential role as a prognostic biomarker for many cancers.

Unlike the pan-endothelial markers, CD31, CD34, and von Willebrand factor, CD105 is a marker of activated endothelium and participates in angiogenesis. Concerns about whether high MVD in the tumor is associated with this poor prognosis are most likely due to the inefficient use of pan-endothelial markers in identifying angiogenic endothelial cells. The prognostic value of MVD is quite high for patients with breast cancer, gynecological cancer, head and neck squamous cell carcinoma.[17]

Based on a study conducted by Xiaoli Hu et al, no statistical significance was found in the relationship between the level of MVD assessed by anti-CD31, CD34 or CD105 and the prognosis of cervical cancer patients for OS or DFS. This suggests that CD34 has better sensitivity and specificity than factor VIII for endothelial cells activated by regional tumor angiogenesis. Uzzan et al. in their study found that microvessel counts evaluated with anti-CD31 or anti-CD34 were approximately 30% higher than factor VIII. Therefore, it is considered that there is no statistical significance of the relationship between the number of MVDs assessed by other biomarkers including CD31, CD34 and CD105, and the prognosis of cervical cancer patients is limited by several related studies.[16]

On the other hand, two studies have shown that microvessel density increases progressively with the degree of CIN and may reflect signals generated by dysplastic cells. Satfl and Mattingly in their study have suggested that the neovascularization observed in cases of CIS progresses to invasive disease. Microvessel density is an independent prognostic parameter for disease-free survival in patients with stage IB and IIA cervical cancer. Obermair showed that patients with stage IB cervical cancer and negative lymph nodes, with MVD <20, had a 5-year survival probability of 94%. Meanwhile, patients also with negative lymph nodes, with MVD >20, have a 75% chance of survival.[18]

Dinh et al. in his study studied a group of 22 patients with stage IB cervical cancer and found that tumor size and number of microvessels were predictors of early recurrence in this group. Cooper et al. studied patients with locally advanced cervical cancer and found that this group of patients had worse 5-year survival and increased local recurrence suggesting an association of the known role of angiogenesis in driving tumor growth and progression.[19]

For patients with MVD greater than 20, with a significant decrease in survival

for patients with stage IIA cervical cancer and a trend for worse survival for patients with IIB cervical cancer. In conclusion, the results of this study indicate that MVD alone is a poor prognostic factor, with increased recurrence rates in tumors with high MVD, and when related to patient age, MVD is a more favorable factor.[10]

The prognostic value and predictive value of NACT (Neoadjuvant Chemotherapy) sensitivity of different microvessel endothelium markers (such as CD31 and CD105) are not the same. Although many studies have been conducted to determine the relationship between microvasculature and prognosis, they present conflicting findings. The study results were likely influenced by differences in medical treatment received and different markers of tumor angiogenesis.[20]

The study conducted by Randall, et al. have shown that CD31-MVD, is an independent prognostic factor in patients with high-risk early-stage cervical cancer. However, different findings were obtained for CD105. CD105-MVD was identified as a significant and independent predictor of recurrence in prostate cancer patients after radical prostatectomy with neoadjuvant hormonal therapy. CD105-MVD is associated with metastasis-free survival and cause-specific survival in patients with urothelial cancer. This inverse prognostic value may imply varying biological potential of different markers of tumor angiogenesis in different types of solid tumors.

Conclusion

In recent times, the handling of cervical cancer cases has progressed both in terms of prevention, early detection and treatment. Early detection and early treatment will improve the prognosis of this disease. Tumor angiogenesis is an important process in which tumor cells can grow, invade and metastasize. The process of angiogenesis is activated in response to hypoxia, which, together with the presence of nutritional deprivation conditions, can amplify the expression of inflammatory signals and cytokines that recruit vascular cells for tumor vascular plexus formation. Microvessel Density (MVD) calculation is a method that can be used to evaluate intratumor angiogenesis in cancer and as a determining factor in the prognosis of cervical cancer with a fairly high prognostic value.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.
2. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. New England Journal of Medicine. 2020 Oct 1;383(14):1340–8.
3. World Health Organization. Cervical Cancer. WHO . 2022.
4. Madeddu C, Sanna E, Nemolato S, Mulas O, Oppi S, Scartozzi M, et al. Pathogenic and Prognostic Roles of Paraneoplastic Leukocytosis in Cervical Cancer: Can Genomic-Based Targeted Therapies Have a Role? A Literature Review and an Emblematic Case Report. Diagnostics. 2022 Aug 7;12(8):1910.
5. Hattori S, Yoshikawa N, Mogi K, Yoshida K, Yoshihara M, Tamauchi S, et al. Significance of Concurrent Chemoradiotherapy as Primary Treatment in Patients with Metastatic Cervical Cancer. Current Oncology. 2021 Apr 29;28(3):1663–72.
6. Leek RD. The prognostic role of angiogenesis in breast cancer. Anticancer Res. 2001;21(6B):4325–31.
7. Jilaveanu LB, Puligandla M, Weiss

SA, Wang XV, Zito C, Flaherty KT, et al. Tumor Microvessel Density as a Prognostic Marker in High-Risk Renal Cell Carcinoma Patients Treated on ECOG-ACRIN E2805. Clinical Cancer Research. 2018 Jan 1;24(1):217–23.
8. Naccarato AG, Viacava P, Bocci G, Fanelli G, Aretini P, Lonobile A, et al. Definition of the microvascular pattern of the normal human adult mammary gland. J Anat. 2003 Dec;203(6):599–603.
9. Weidner N, Semple JP, Welch WR, Folkman J. Tumor Angiogenesis and Metastasis — Correlation in Invasive Breast Carcinoma. New England Journal of Medicine. 1991 Jan 3;324(1):1–8.
10. Hu X, Liu H, Ye M, Zhu X. Prognostic value of microvessel density in cervical cancer. Cancer Cell Int. 2018 Dec 3;18(1):152.
11. Winata IGS, Budiana ING, Jawi IM, Suwiyoga K. Neoadjuvant Chemotherapy in Stadium IB3, IIA2 and IIB Cervical Cancer a Narrative Review. Biomedical and Pharmacology Journal. 2022 Jun 30;15(2):901–10.
12. Andrijono. Kanker Serviks. 5th ed. Jakarta: Divisi Onkologi. Departemen Obstetri-Ginekologi. Fakultas Kedokteran Universitas Indonesia; 2016.
13. Callahan TL, Caughey AB. Blueprints Obstetrics & Gynecology. 2018.
14. Berek JS, Berek DL. Berek & Novak's Gynecology. 2020.
15. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Williams Gynecology. 2016.
16. Bielenberg DR, Zetter BR. The Contribution of Angiogenesis to the Process of Metastasis. The Cancer Journal. 2015 Jul;21(4):267–73.
17. Rajabi M, Mousa S. The Role of Angiogenesis in Cancer Treatment. Biomedicines. 2017 Jun 21;5(4):34.
18. Adair TH, Montani JP. Overview of Angiogenesis. 2010.
19. Jiang X, Wang J, Deng X, Xiong F, Zhang S, Gong Z, et al. The role of microenvironment in tumor angiogenesis. Journal of Experimental & Clinical Cancer Research. 2020 Dec 30;39(1):204.
20. Bożyk A, Wojas-Krawczyk K, Krawczyk P, Milanowski J. Tumor Microenvironment—A Short Review of Cellular and Interaction Diversity. Biology (Basel). 2022 Jun 18;11(6):929.