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REVIEW ARTICLE

Prognostic significance of tumor angiogenesis markers in advanced cervical cancer undergoing chemotherapy

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ABSTRACT

Cervical cancer is the second leading cause of cancer-related deaths among women worldwide. Despite advancements in screening programs and vaccination efforts, a significant proportion of patients present with advanced-stage disease, characterized by severe manifestations and a poor prognosis. Clinical evidence highlights substantial variability in the sensitivity of chemotherapy regimens among cervical cancer patients, often resulting in suboptimal therapeutic outcomes and increased risk of complications. This underscores the need for reliable molecular markers to predict prognosis and optimize therapy. Angiogenesis plays a pivotal role in the development and progression of solid tumors, including cervical cancer. Key tumor angiogenesis markers, such as vascular endothelial growth factor (VEGF) and its receptor (VEGFR), are critical in driving tumor progression in advanced cervical cancer. Studies have demonstrated significant correlations between VEGF levels and important prognostic parameters, including tumor size, metastasis, and chemotherapy response. Consequently, tumor angiogenesis markers like VEGF and VEGFR hold potential as valuable predictive tools to guide the management of advanced cervical cancer, particularly in patients undergoing chemotherapy.

1. Introduction

Cervical cancer, a malignancy of the cervix, ranks as the third most common cancer among women and the second leading cause of cancer-related deaths globally, underscoring its significance as a primary public health concern (Brisson & Drolet, 2019; Pimple & Mishra, 2019). Advances in screening technologies and the widespread adoption of effective cervical cancer vaccines have significantly improved the early detection and prevention of pre-neoplastic lesions, thereby reducing the incidence of cervical cancer (Pimple & Mishra, 2019; Zhang *et al.,* 2020). The introduction of the Pap smear as a standard screening tool has been particularly impactful, with data demonstrating a marked reduction in the prevalence of advanced-stage cases and related mortality (Foran & Brennan, 2015; Pierre-Victor *et al.,* 2018). Despite these advancements, many patients continue to present at healthcare centers with advanced-stage disease (stage IVB or higher) or large tumors in earlier stages, often due to limited access to preventive measures and sociodemographic challenges. Studies indicate stark disparities in survival outcomes, with five-year survival rates of approximately 80% for early-stage cervical cancer, compared to only 20%-42% for advanced-stage disease (Çakır *et al.,* 2021).

In Asia, chemotherapy followed by surgery remains a primary treatment approach for advanced cervical cancer, while concurrent chemoradiotherapy (CCRT) is increasingly recognized as the standard of care. Additionally, neoadjuvant chemotherapy (NAC) has been introduced to improve treatment

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outcomes in advanced cases (Todo & Watari, 2016; Weng *et al.,* 2022). However, significant variability in patients' chemosensitivity continues to pose challenges, leading to ineffective therapies and an increased risk of complications (Barut *et al.,* 2015; Scatchard *et al.,* 2013). This highlights the urgent need for reliable molecular markers to predict prognosis and guide personalized treatment accurately.

Angiogenesis, the process of new blood vessel formation, is a critical factor in the growth and progression of solid tumors, including cervical cancer. Multiple studies have established a strong correlation between angiogenesis and poor prognosis in solid tumors, particularly cervical malignancies (Eskander & Tewari, 2014; Ramesh *et al.,* 2020; Tomao *et al.,* 2014; Yetkin-Arik *et al.,* 2021). Vascular endothelial growth factor (VEGF) and its receptor (VEGFR), key mediators of angiogenesis, have been implicated in aggressive tumor behavior, including enhanced vascular invasion, metastasis, and poor clinical outcomes (Eskander & Tewari, 2014; Yetkin-Arik *et al.,* 2021).

While several studies have investigated the role of angiogenesis markers in cervical cancer, their findings have often been inconsistent, and limited research has focused on their prognostic significance in advanced tumors treated with chemotherapy. This review aims to evaluate the utility of tumor angiogenesis markers, specifically VEGF and VEGFR, as prognostic factors in advanced cervical cancer undergoing chemotherapy. This review provides insights into their potential to guide clinical decision-making and improve patient outcomes by synthesizing current evidence.

2. Methods

All references used in this literature review were searched and retrieved in several databases such as PubMed (MEDLINE), Google Scholar, and Science Direct (Elsevier) with the following keywords: advanced cervical cancer, angiogenesis, marker, chemotherapy, and prognosis.

The inclusion criteria were described as follows: (1) Articles published in English and Bahasa Indonesia, (2) Articles published in at least the last 10 years, (3) Studies that reported any findings related to angiogenesis marker (VEGF/VEGFR), and prognosis of patients with advanced stage and have been treated with the chemotherapy regimen. Exclusion criteria were (1) Review articles, such as narrative reviews and systematic reviews, and (2) Full-text versions were not available.

Through the search and screening process, 25 studies were identified, of which seven were selected as the primary references for this review. These studies were evaluated for their relevance and contribution to the understanding of angiogenesis markers as prognostic factors in advanced cervical cancer treated with chemotherapy.

3. Results

3.1. Chemotherapy in advanced cervical cancer

Cervical cancer is characterized by invasive growth, involving continuous tumor proliferation and local spread through newly formed lymphatic and blood vessels. Surgical resection often fails to eliminate cancer cells that infiltrate capillaries and lymphatic channels, leading to a high risk of postoperative recurrence and metastasis (Kurmyshkina *et al.,* 2015). Neoadjuvant chemotherapy (NAC) has emerged as a standard preoperative treatment, effectively reducing tumor size, inhibiting lymphangiogenesis and angiogenesis, and eradicating locally infiltrated cancer cells, thus facilitating complete surgical resection (Shang *et al.,* 2020). Two approaches to NAC include internal iliac arterial infusion chemoembolization and systemic intravenous chemotherapy. Internal iliac arterial infusion enhances the local concentration and retention of chemotherapeutics within tumor tissues, making it more effective than systemic intravenous administration (Abdalla *et al.,* 2015).

Beyond its cytotoxic effects, arterial infusion chemoembolization induces ischemic damage to cancer cells by embolizing tumor-nourishing blood vessels. Platinum-based drugs, such as cisplatin or carboplatin, activate the mitochondrial apoptotic pathway via Caspase-9, signaling downstream molecules (Caspase-7, Caspase-8) and culminating in Caspase-3 activation, which mediates apoptosis (Baharara *et al.,* 2016; Tian *et al.,* 2014). NAC has been integrated into the standard treatment for cervical malignancies to reduce tumor volume and extent, improve local treatment outcomes, and convert inoperable cases into operable ones (Li *et al.,* 2021; Nwankwo *et al.,* 2020). Additionally, combining chemotherapy and radiotherapy (chemo sensitization) enhances tumor radiosensitivity by synchronizing tumor cells to a radio-sensitive cell cycle phase, resulting in improved outcomes.

3.2. Angiogenesis in advanced cervical cancer

The role of angiogenesis in cervical cancer progression is well-documented. Tumor-induced angiogenesis disrupts the balance between pro-angiogenic factors (e.g., VEGF, fibroblast growth factor [FGF], and platelet-derived growth factor [PDGF]) and anti-angiogenic factors (e.g., angiostatin and endostatin), creating a pro-angiogenic environment conducive to neovascularization (Dang *et al.,* 2017; Pinheiro *et al.,* 2015; Sawada *et al.,* 2019; Yoshida *et al.,* 2018). Angiogenic processes result in the proliferation

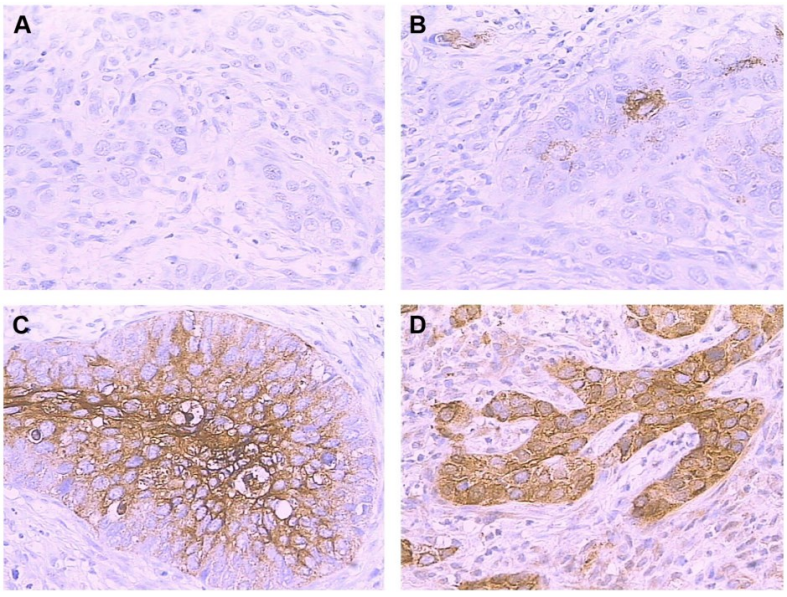

Figure 1. The immunohistological visualization showing VEGF expression in advanced cervical cancer lesions with A). negative expression; B). weak expression; C). moderate expression; and D). strong expression (Zhu *et al.,* 2016)

of microvessels within malignant growths, granting cancer cells access to the vascular system and enabling metastatic spread. VEGF and its receptor (VEGFR) are key mediators of tumor angiogenesis, with dysregulation of their expression linked to tumor growth, metastasis, and patient survival (Dang *et al.,* 2017; Pinheiro *et al.,* 2015; Sawada *et al.,* 2019; Yoshida *et al.,* 2018).

VEGF, a multifunctional cytokine, enhances endothelial cell proliferation, migration, and permeability, directly contributing to tumor invasion, growth, and metastasis by facilitating the formation of capillary networks around the tumor (Du *et al.,* 2014). Immunohistological analyses of advanced cervical cancer lesions post-radio-chemotherapy have revealed increased VEGF expression within the cytoplasm of cancer cells, further underscoring its role in tumor progressions (Figure 1) (P. F. Zhu *et al.,* 2016).

3.3. Tumor Neoangiogenesis Marker as Prognostic Factors

Several studies (Table 1) have evaluated VEGF and VEGFR levels in patients with advanced cervical cancer treated with chemotherapy, consistently demonstrating a correlation between VEGF levels and patient prognosis. Altered VEGF expression has been implicated in tumor growth, angiogenesis, and adverse clinical outcomes (Choi *et al.,* 2008; Du *et al.,* 2014; Gao *et al.,* 2020; Kfouri *et al.,* 2019; X. Li *et al.,* 2022; Rahmani *et al.,* 2018; P. F. Zhu *et al.,* 2016).

Li *et al.* (2022) reported that VEGF correlated with therapeutic response in cervical cancer patients. Furthermore, combining chemotherapy with radiotherapy using a 3D-image-guided after-loading intra-David Radiotherapy technique showed that VEGF levels decreased after administration of combination therapy. This indicates that combining chemotherapy regimens with other anticancer regimens can improve therapeutic responses, especially those related to the mechanism of tumor angiogenesis. Du *et al.* (2014) observed that elevated VEGF levels in tumors larger than 4 cm correlated with disease progression and adverse effects like myelosuppression. Similarly, Gao *et al.* (2020) and Kfouri *et al.* (2019) further confirmed the predictive value of VEGF, with Kfouri *et al.* specifically linking positive VEGF status to significant tumor regression (>50%) in response to NAC. A study by Zhu *et al.* (2016) also reported that VEGF levels have good diagnostic value for measuring and predicting response to post-chemotherapy therapy in cases of advanced cervix carcinoma.

Both VEGF and VEGFR can affect cancer cell development through the mechanism of tissue hypoxia found in advanced cancer lesions. Hypoxic cancer cells are generally resistant to radiotherapy and chemotherapy. In hypoxic tissues, the increase in VEGF that causes angiogenesis is caused by the primary mediator, hypoxia-inducible factor-1α (HIF-1α), a crucial transcription factor that is highly active in tumor cells and is known to control cellular metabolism and protein pathways under particular hypoxic stimulation. Increased HIF-1α will lead to increased gene regulation and expression of VEGF and VEGFR in cancer cells (Tang *et al.,* 2021; Zhu *et al.,* 2016). HIF-1α is also further influenced by mediators such as COX-2, thymosin β4, and other pro-inflammatory mediators (Zuo *et al.,* 2013). Many chemotherapies also affect the proliferation and permeability of cancerous tissue. It might explain the decrease in VEGF levels after the administration of

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Table 1. Studies evaluated tumor neoangiogenesis marker as a prognostic factor in advanced cervical cancer treated with chemotherapy

Author, year	Study design	Total population	Marker	Result
(Kfouri *et al.,* 2019)	An observational study (case series)	40	VEGF and VEGFR-2	Only the positive expression of VEGF was linked to a satisfactory clinical response for chemotherapeutic treatment (p=0.0157). Patients with advanced cervical cancer who had neoadjuvant chemotherapy had VEGF expres sion alone as a key indicator of a favorable response.
(Li *et al.,* 2022)	An observational study (case-control)	67	VEGF	The change in tumor diameter between before and after neoadjuvant chemotherapy and 3D-image-guided after loading intracavitary radiation was positively correlated with VEGF level (p<0.05).
(Rahmani *et al.,* 2018)	Observational study	65	Her-2, VEGF	Her-2 and VEGF overexpression/ upregulation are associated with a poor prognosis and may be crucial in the onset and metastasis of cervical cancer. The expression pattern of the VEGF protein did not significantly change between the various grades and stages of tumors (p > 0.05).
(Choi *et al.,* 2008)	Observational study	29	VEGF	VEGF positivity was an independent predictor of poor response (p=0.032). Additionally, individuals with VEGF-positive tumors had a substantially lower rate of progression-free survival rate (p=0.033). Therefore, preoperative evaluation of VEGF expression may offer additional information to help predict poor prognosis in the patient and a low chance of responding to neoadjuvant chemotherapy.
(P. F. Zhu *et al.,* 2016)	Observational study	43	VEGF, HIF-1α	Both VEGF and HIF-1α levels and expression are potential biomarkers for preoperative radiochemotherapy (PRCT) in locally advanced cervical cancer (LACC) patients.
(Gao *et al.,* 2020)	Observational study	108	VEGF, Cyclin A, CDK2, SCCA, CEA	The expressions of Cyclin A, Cyclin-dependent kinase 2 (CDK2) mRNA and human squamous cell carcinoma antigen (SCCA), carcinoem bryonic antigen (CEA), and VEGF after treatment were significantly lower compared to those before treatment of chemotherapy (p< 0.05).
(Du *et al.,* 2014)	Observational study	37	VEGF	Based on multivariate analysis, VEGF level was the risk factor affecting the therapeutic outcome in tumor size >4 cm.

chemotherapy in advanced cancer cases, which are still sensitive (Parida *et al.,* 2016; Patel *et al.,* 2020).

However, in most cases of advanced cervical cancer, chemotherapy is generally ineffective due to resistance. The correlation of changes in VEGF levels in these cases cannot be explained with certainty. Moreover, previous studies have shown that increased angiogenesis by VEGF induction in cancer tissue leads to the formation of abnormal vascular tissue structures. This results in decreased distribution of chemotherapy to the lesion site while maintaining adequate oxygen flow. In addition, HIF-1α can also increase the expression of some anti-apoptotic proteins that prevent apoptosis of abnormal vascular tissue (Rizzuto *et al.,* 2020). In addition, according to research on VEGF levels in breast cancer, high levels of VEGF in tumors are linked to poor response to chemotherapy drugs like tamoxifen and increased risk of metastasis. This is because VEGF stimulates endothelial cell proliferation, which results in the expression of proteins that make tumors resistant to drugs, including glutathione-S-transferase (GST) (Lv *et al.,* 2018).

On the other hand, the influence of VEGF receptor or VEGFR levels on cervical cancer patients' prognoses has only been examined in a small number of research. Earlier observational studies demonstrated

that baseline parameters, including age and tumor size, as well as mRNA expression and VEGFR2 expression levels, may influence the radio sensitivity and chemosensitivity of cervical cancer patients. The same study also revealed that VEGFR2 level predicted tumor prognosis (Du *et al.,* 2014; Liu *et al.,* 2013).

A study also investigated the immunohistochemistry expression of VEGF and its relationship to the 5-fluorouracil and cisplatin response. Positive VEGF cases had a substantial therapeutic impact (p=0.0031), with response rates of 75% (12/16) and 16.7% (2/14) for positive and negative VEGF cases, respectively. Patients who tested positive for VEGF also responded better to 5-fluorouracil and cisplatin-based neoadjuvant treatment. The enhanced drug release, increased vascular permeability, and improved local performance in regions of tumor neoangiogenesis may be the causes of the association between chemotherapy response and VEGF production (Kfouri *et al.,* 2019).

4. Discussion

As outlined earlier, the primary angiogenesis markers, VEGF and VEGFR, play a pivotal role in cervical cancer development and progression. VEGF is secreted in response to hypoxia, acidosis, mechanical stress, and increased VEGFR expression in cancer cells. Tumor hypoxia triggers the production of hypoxia-inducible factor-1 (HIF-1), which forms a complex to stimulate growth factors such as VEGF (A-F), particularly VEGF-A. VEGF-A is crucial in enhancing vascular permeability and angiogenesis. While all VEGF subtypes contribute to angiogenesis, VEGF-A is widely recognized as the most significant factor in tumor angiogenesis. In contrast, VEGF-C is associated with lymphatic vessel hyperplasia, which facilitates the spread of solid tumors, including cervical and ovarian cancers (Apte *et al.,* 2019).

The role of angiogenesis in cervical cancer has been extensively studied over time. Recent findings, however, have highlighted its relevance in advanced cervical lesions, particularly in influencing responses to chemotherapy. Several trials evaluating anti-VEGF agents, such as bevacizumab, sunitinib, pazopanib, brivanib, and imatinib, have demonstrated promising clinical outcomes (Tomao *et al.,* 2014).

Despite these advancements, the number of studies addressing angiogenesis in advanced cervical cancer remains limited. Available research suggests that changes in VEGF and VEGFR levels could serve as indicators of therapeutic response in advanced cases receiving chemotherapy and perhaps even in those undergoing radiotherapy. However, many studies lack robust clinical significance (e.g., risk ratios exceeding 2 for VEGF level relative to prognostic parameters) (Tomao *et al.,* 2014).

Another significant challenge is the heterogeneity among studies, complicating direct comparisons. Differences in study populations, VEGF cutoff values, and cervical cancer histological subtypes contribute to these inconsistencies. This heterogeneity underscores the need for standardized methodologies and more extensive, more clinically relevant studies to determine the precise role of VEGF in advanced cervical cancer. Furthermore, the rising incidence of chemotherapy resistance necessitates a reevaluation of management strategies, warranting further investigation into VEGF's potential as a therapeutic target. In this review, only a limited number of studies evaluated VEGF and VEGFR levels as prognostic markers for cervical cancer. Additionally, few studies provided clear prognostic parameters, limiting the ability to derive comprehensive conclusions (Tomao *et al.,* 2014).

Nevertheless, VEGF levels have significant implications for monitoring treatment responses. They can be utilized to compare the effectiveness of different chemotherapy regimens and gauge therapeutic outcomes. As previously discussed, combining chemotherapy with radiotherapy or other treatment modalities significantly impacts VEGF levels and patient outcomes. Further research focusing on these interactions could enhance our understanding of VEGF's role in improving cervical cancer prognosis and treatment strategies.

5. Conclusions

Chemotherapy remains a cornerstone of treatment for advanced cervical cancer, but decreasing chemosensitivity poses a significant challenge. Among the various tumor angiogenesis markers identified, VEGF and VEGFR stand out as key mediators that not only drive cancer progression but also influence patient prognosis. Most studies demonstrate a positive correlation between VEGF levels and prognostic parameters, as well as treatment response. Elevated VEGF levels are often associated with reduced chemosensitivity, whereas lower levels correlate with improved therapeutic outcomes. These findings suggest that angiogenesis markers, particularly VEGF and VEGFR, hold potential as prognostic indicators for advanced cervical cancer treated with chemotherapy. However, the precise mechanisms linking VEGF levels to diminished chemosensitivity remain unclear. Additionally, the limited number of studies exploring the role of angiogenesis markers in advanced cervical cancer and their relationship with chemotherapy regimens highlights a significant gap in the current understanding. Future research should focus on elucidating the underlying mechanisms of VEGF-mediated resistance and expanding the clinical

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evaluation of angiogenesis markers. This will be crucial in optimizing therapeutic strategies and improving outcomes for patients with advanced cervical cancer.

Conflict of interest

All authors have no conflict of interest in this article.

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