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Review Article

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Gastric Cancer and Angiogenesis: Is VEGF a Useful Biomarker to Assess Progression and Remission?

Filipa Macedo[1], Kátia Ladeira[2,3,4], Adhemar Longatto-Filho[3,4,5,6], Sandra F. Martins[3,4,7]

[1]Portuguese Oncology Institute - Coimbra, Coimbra, Portugal
[2]Portuguese Oncology Institute - Lisbon, Lisbon, Portugal
[3]Life and Health Science Research Institute, School of Health Sciences, University of Minho, Braga, Portugal
[4]ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Braga, Portugal
[5]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil
[6]Laboratory of Medical Investigation 14, Faculty of Medicine, University of São Paulo, São Paulo, Brazil
[7]Surgery Department, Coloproctology Unit, Braga Hospital, Braga, Portugal

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Correspondence to
Sandra F. Martins
Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
Tel: + 351-933-361-345
Fax: +351-253-604-847
E-mail: sandramartins@med.uminho.pt

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Gastric cancer (GC) has high mortality owing to its aggressive nature. Tumor angiogenesis plays an essential role in the growth, invasion, and metastatic spread of GC. The aim of this work was to review the angiogenic biomarkers related to the behavior of GC, documented in the literature. A search of the PubMed database was conducted with the MeSH terms: "Stomach neoplasms/blood [MeSH] or stomach neoplasms/blood supply [MeSH] and angiogenic proteins/blood [Major]". A total of 30 articles were initially collected, and 4 were subsequently excluded. Among the 26 articles collected, 16 examined the role of vascular endothelial growth factor (VEGF), 4 studied endostatin, 3 investigated angiopoietin (Ang)-2, 2 studied the Ang-like protein 2 (ANGTPL2), and 1 each examined interleukin (IL)-12, IL-8, and hypoxia inducible factor. Regarding VEGF, 6 articles concluded that the protein was related to lymph node metastasis or distant metastases. Five articles concluded that VEGF levels were elevated in the presence of GC and decreased following tumor regression, suggesting that VEGF levels could be a predictor of recurrence. Four articles concluded that high VEGF levels were correlated with poor prognosis and lower survival rates. Ang-2 and ANGTPL2 were elevated in GC and associated with more aggressive disease. Endostatin was associated with intestinal GC. VEGF is the most extensively studied angiogenic factor. It is associated with the presence of neoplastic disease and lymph node metastasis. It appears to be a good biomarker for disease progression and remission, but not for diagnosis. The data regarding other biomarkers are inconclusive.

Keywords: Angiogenic proteins; Stomach neoplasms; Lymph nodes; Neoplasm metastasis; Vascular endothelial growth factor A; Recurrence

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer, responsible for more than 800,000 deaths worldwide each year. Despite the decline in mortality rates observed in recent decades, GC remains second only to lung cancer as a cause of cancer-related deaths. More than one million people are newly diagnosed with GC each year, imposing a heavy burden on world health services [1].

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The 5-year survival rates are 50% in patients with advanced cancer and 95% in patients who are diagnosed early [1]. The high mortality rate is related to the late diagnosis owing to non-specific manifestations of the disease in the early phases, as well as to its aggressive nature, which is associated with mutations of various genes and abnormalities in several growth factors and their receptors [2].

Tumor angiogenesis and lymphangiogenesis play an essential role in the growth, invasion, and metastatic spread of solid neoplasms by facilitating the delivery of oxygen, nutrients, and growth factors to tumor cells. Angiogenesis is regulated by certain essential molecules. Vascular endothelial growth factor (VEGF) is one of the most important factors driving tumor angiogenesis. The VEGF family consists of 7 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor (PlGF). These proteins act through specific tyrosine kinase receptors (VEGF receptor 1 [VEGFR1], VEGFR2, and VEGFR3), expressed primarily on endothelial cells. Most of these molecules are transported by platelets and released into serum after platelet degranulation during blood clotting; only a small proportion circulate freely in the bloodstream [3].

In 1971, Folkman [4] established the importance of angiogenesis in tumorigenesis. He suggested that tumor growth and expansion are closely related to the development of a network of blood vessels within a tumor. Thus, the blocking of angiogenesis can be a good strategy to prevent tumor growth.

Endostatin is an endogenous tumor angiogenesis inhibitor. It inhibits tumor angiogenesis and metastasis by limiting tumor blood supply, thereby depriving tumors of nutrients, and has been considered as a potential anticancer marker in the treatment of malignant tumors [5].

Angiopoietins (Ang) are thought to be important factors in vascular maturation and stability during angiogenesis [6]. Of the 4 Ang proteins identified (Ang-1 to Ang-4), the best characterized are Ang-1 and Ang-2. They are both ligands of Tie-2, a receptor expressed on endothelial cells, and they play critical roles in angiogenesis. Binding of Ang-1 to Tie-2 maintains and stabilizes mature vessels by promoting interactions between endothelial cells and the surrounding extracellular matrix. Ang-2 shows context-dependent, proangiogenic, and antiangiogenic activities [7].

In recent years, a significant focus on the identification of biomarkers for early detection of GC has been observed. In the present report, the authors performed a literature review regarding the role of angiogenic biomarkers in GC.

SEARCH METHODS

A PubMed search was conducted focusing on angiogenesis in GC. The MeSH database was searched with the terms: “Stomach neoplasms/blood [MeSH] or stomach neoplasms/blood supply [MesH] and angiogenic proteins/blood [Major]”.

A total of 30 articles were initially collected. Four articles were subsequently excluded from this review: one was excluded because the subject of the study was neuroendocrine carcinomas, and no GCs were examined; another paper was excluded because it was a letter to the editor; another because the article was written in Romanian; and another was excluded

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because it evaluated the most suitable compartment for the assessment of VEGF, and thus it did not study the molecule itself. Ultimately, 26 studies were included in the analysis.

TUMOR MARKERS

The main results of the selected studies are listed in **Table 1**. Conventional tumor markers do not allow diagnosis of GC with adequate sensitivity and specificity; their use is limited to prognosis and follow-up recommendations [8]. However, several studies presently underway are attempting to establish new molecules as tumor markers [9]. Currently, preoperative staging relies on imaging studies, but these modalities cannot confirm or exclude the presence of metastatic lymph nodes. This is a very important issue in determining the ideal treatment for an individual, such as the choice of gastrectomy vs. submucosal resection [10,11].

VEGF FAMILY

In the study of Wang et al. [10], the level of VEGF-C in serum was demonstrated to be higher in patients with lymph node metastasis (P<0.001) and with distant metastasis (P<0.001). VEGF-C and VEGF-D are both ligands for VEGFR-3 on the surface of lymphatic endothelial cells and act as regulators of lymphangiogenesis; these had been reported to be important factors in stimulating lymphangiogenesis and lymphatic metastasis [12]. Similarly, Tsirlis et al. [11] verified that in the preoperative period, VEGF-C levels were lower and VEGF-D levels were higher in patients with cancer when compared with controls (P<0.001). In the postoperative period, VEGF-C levels increased and VEGF-D levels decreased compared with the preoperative level (P<0.001). Serum VEGF-C and VEGF-D levels were identified as statistically significant independent predictors of the presence of GC (P<0.001). The VEGF-C/VEGF-D ratio was found to be the most potent predictor of malignancy (P<0.001). Wang et al. [13] found that the serum VEGF-C level was significantly higher in patients with GC than in controls (P<0.001). VEGF-C positive expression was higher in GC tissue (P=0.001) and in areas of higher lymph vessel density (P<0.001). There was a positive correlation between serum VEGF-C and lymph node metastasis (P<0.001). The group of patients with VEGF-C positive expression had a shorter mean survival time. High expression of VEGF-C may be used as a biomarker for the development of GC and may predict unfavorable survival rates. It appears that VEGF-C produced by cancer cells may increase the expression of VEGFR-3 on lymphatic endothelial cells and promote the formation of new lymphatic vessels [13].

As part of a search for angiogenic activators and their receptors, Kikuchi et al. [14] concluded that VEGF levels were higher in patients than in controls, but interestingly, VEGFR-1 and VEGFR-2 levels were lower. VEGF showed the greatest sensitivity and specificity as a marker associated with intestinal-type cancer, while VEGFR-1 showed the highest sensitivity and specificity for early GC and VEGFR-2 showed the greatest sensitivity and specificity for diffuse-type and advanced cancer.

VEGF is stored in alpha granules and released upon platelet activation during clotting, while peripheral blood cells such as platelets, granulocytes, and lymphocytes also express VEGF [15]. Accordingly, some researchers have used VEGF per platelet count to correct for the variation of serum VEGF levels in cancer patients with different platelet counts. Seo et al.

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Table 1. Main results of selected studies

Study/author	Year	No.	Molecule	Conclusion	Values
Wang et al. [10]	2012	80 patients 0 controls	VEGF-C	Preoperative diagnosis of lymph node metastasis and distant metastasis (P<0.001).	- Cut-off value of 542.5 pg/mL. - Sensitivity of 82.5%, specificity of 92.3%.
Tsirlis et al. [11]	2010	40 patients 40 controls	VEGF-C and VEGF-D	Detection and staging in GC (P<0.001).	- VEGF-C cut-off value 1.1 pg/mL, sensitivity 83%, specificity 70%. - VEGF-D cut-off value 370 pg/mL, sensitivity 88%, specificity 73%. - VEGF-C/D ratio cut-off value 2.7, sensitivity 88%, specificity 75%.
Kikuchi et al. [14]	2011	164 patients 164 controls	VEGF, VEGFR-1, and VEGFR-2	VEGF level is elevated in patients with GC, VEGFR-1, and VEGFR-2 are reduced compared to controls.	- VEGF cut-off value of 415 pg/mL, sensitivity of 63.5%, and specificity of 65.1%, for intestinal type cancer. - VEGFR-1 cut-off value of 46 pg/mL, sensitivity of 60%, and specificity of 58.6%, for early cancer. - VEGFR-2 cut-off value of 8,314 pg/mL, sensitivity of 66.3%, and specificity of 61.6%, for advanced and diffuse type cancer.
	2010	181 patients 113 controls	VEGF	Poor OS and progression-free survival in advanced GC.	
Sheng et al. [17]	2008	92 patients 92 controls	VEGF	It was higher in GC patients than in healthy controls and benign gastric disease. Association with distant metastases, invasion depth of the tumor and tumor stage.	- VEGF cut-off value of 217.79 pg/mL, sensitivity of 40.2%, and specificity of 93.7%, by TR-IFMA.
Wang et al. [13]	2007	80 patients 20 controls	VEGF-C	Lymph node metastasis and poor prognosis.	- Serum VEGF-C cut-off value of 367.5 ng/L, sensitivity of 85%, and specificity of 80%, for GC diagnosis. - Serum VEGF-C cut-off value of 542.5 ng/L, sensitivity of 82.8%, and specificity of 81.8%, for lymph nodes metastasis diagnosis.
Ding et al. [18]	2005	135 patients 48 controls	VEGF-A	Levels were higher in patients with GC (P<0.010) and they decreased following tumor excision (P<0.001).	
Park et al. [19]	2015	381 patients (118 Caucasians +263 Asians) 0 controls	VEGF-A and VEGFR-2/CD31	Caucasians had a median VEGF-A level that was 95% higher than that of Asians (P<0.001). Survival was worse in Caucasians with high VEGFR-2/CD31 levels (P=0.038). These were independent predictors of survival only in Caucasians.	
Villarejo-Campos et al. [3]	2013	59 patients 0 controls	VEGF	Levels decreased after treatment (P<0.010). Preoperative levels were independent prognostic factor.	- Preoperative VEGF values over 761 pg/mL were associated with shorter patient survival.
Vidal et al. [20]	2009	97 patients 20 controls	VEGF	Higher in patients with GC than controls (P=0.002).	- Serum VEGF over 320 pg/mL was the only preoperative predictor of both recurrence and disease-specific survival.
Bilgiç et al. [21]	2015	30 patients 30 controls	VEGF	Correlation with the tumor type classification and the presence of distant tissue invasion.	
Konno et al. [33]	2003	37 patients 10 controls	VEGF	Higher in patients with GC than controls and higher in patients with venous invasion.	
Blank et al. [34]	2015	76 patients 0 controls	VEGF	Prognostic relevance in patients with primary resection (P=0.028).	
Park et al. [35]	2014	147 patients 0 controls	VEGF-A	Higher in patients with R1 vs. R0 resection (P=0.037). Significant independent prognostic factor for survival (P=0.028).	

VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; GC = gastric cancer; OS = overall survival; TR-IFMA = time-resolved immunofluorometric assay; CD31 = cluster of differentiation 31; R1 = circumferential resection with margin involvement; R0 = circumferential resection without margin involvement.

[16] compared advanced GC with early cancer. Serum VEGF levels were higher in advanced cancer, and a positive correlation was observed between serum VEGF and platelet counts in these patients (P<0.001). Overall survival (OS) (P=0.040) and progression-free survival (P=0.010) were shorter in patients with high serum VEGF per platelet count.

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Sheng et al. [17] used a time-resolved immunofluorometric assay (TR-IFMA) to measure VEGF levels in blood, instead of a radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA). Compared with these techniques, TR-IFMA is characterized by lower detection limits and greater specificity, reproducibility, and practicability. Plasma VEGF levels in patients with benign stomach disease were higher than in controls (P=0.040) but lower than the levels in patients with GC (P=0.030). Higher VEGF levels were detected as the disease stage and the invasion depth of the tumor increased P=0.030 and P=0.040, respectively, and in patients with distant metastases P=0.009. There was no significant association between VEGF levels and the presence of lymph node metastasis [17].

Ding et al. [18] reported that VEGF-A levels were significantly higher in both serum and plasma from patients with GC (P<0.010). Surgical excision of tumors resulted in a significant reduction of VEGF-A levels, suggesting that VEGF-A was secreted by the tumor mass.

Park et al. [19] compared gastric carcinoma characteristics and the expression of VEGF-A between Caucasian and Asian patients. Caucasian patients had more proximal tumors, a higher incidence of vascular invasion, a higher incidence of neural invasion, and a more advanced tumor, node and metastasis (TNM) stage. The median level of serum VEGF-A in Caucasian patients was nearly twice that observed in Asian patients, and this value was associated with significantly poorer survival (P<0.001). Serum VEGF-A level was an independent prognostic factor for survival in Caucasian patients but it did not demonstrate prognostic value in Asian patients. Patients with higher VEGFR-2/cluster of differentiation 31 (CD31) levels had significantly worse survival rates. Villarejo-Campos et al. [3] found similar results, and demonstrated that serum VEGF levels decreased after treatment in patients with high-grade cancers (P=0.010), locally advanced cancers (P=0.030), large number of positive regional lymph nodes (P=0.040), and resectable tumors (P<0.010). Preoperative high serum VEGF levels >761 pg/mL were associated with shorter patient survival. Preoperative serum VEGF and the number of involved lymph nodes were independent prognostic factors. Preoperative serum VEGF-C values showed conflicting results.

Vidal et al. [20] evaluated the preoperative serum VEGF and urokinase-type plasminogen activator (uPA) levels in patients undergoing GC resection. Serum levels of VEGF in patients with GC were significantly higher than in controls (P=0.002). Higher preoperative serum VEGF levels were associated with advanced disease (advanced TNM stage, perineural invasion, and high lymph node ratio), a lower probability of recurrence-free status (P=0.033), and shorter disease-specific survival (P=0.004). No significant findings were observed in relation to serum uPA as a prognostic factor.

Other studies corroborated the value of VEGF-A as a GC biomarker. For example, Bilgiç et al. [21] found that serum levels of VEGF were correlated with tumor type classification and the presence of distant tissue invasion, and Ilhan et al. [22] demonstrated a statistically significant increase in VEGF levels directly proportional to the cancer stage (P<0.001). Significantly higher VEGF levels were found in patients with cancer than in healthy controls, and the increased VEGF levels were not related to infection (P>0.050). Levels of malondialdehyde, a reactive compound that occurs naturally in situations of oxidative stress, were higher both in patients with GC compared with healthy controls and in patients with cancer and infection compared with those with cancer without infection (P<0.001). Levels were also significantly elevated in cases of metastasis and invasion of other tissues (P<0.001).

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ANG/ENDOSTATIN FAMILY

Procalcitonin and C-reactive protein levels were significantly higher in patients with cancer and infection than in patients with GC without infection, and were significantly higher in all GC groups than in the control group (P<0.001) [22]. Masiak et al. [23] observed a correlation between the histological differentiation and serum concentrations of endostatin (higher grades demonstrated higher concentrations of endostatin). However, the same was not true for epidermal growth factor (EGF) serum concentrations. The difference between the concentrations of endothelial growth factor (EGF) and endostatins in controls and patients were not statistically significant.

Ang are ligands of the endothelial cell surface receptor Tie-2. They inhibit Tie-2 and act as negative regulators of angiogenesis [7]. Wang et al. [24] performed a review of studies of endostatin. The meta-analysis showed an increased level of endostatin in patients with GC (P<0.001), a lower serum endostatin level in lower grade tumors (P<0.001), and a higher serum endostatin level in lymph node invasion (P<0.001). These results suggest that serum endostatin levels might be related to the aggressiveness of GC, could contribute to lymph node metastasis, and could be an important prognostic biomarker in predicting the survival of patients with metastatic GC.

Koç et al. [25] suggested that serum levels of endostatin were correlated with the histologic classification of gastric tumors because higher endostatin levels were observed in intestinal type than in diffuse type tumors. Additionally, Woo et al. [26] concluded that pretherapeutic serum endostatin (P<0.001) and VEGF (P<0.001) levels were higher in patients with GC. The serum endostatin (P<0.001) and VEGF (P=0.001) levels were significantly higher in patients with metastasis than in patients without distant metastasis. The levels of endostatin (P<0.001) and VEGF (P=0.002) were significantly correlated with the presence of distant metastases. The most significant prognostic factor for survival was the disease stage, but patients with a serum endostatin level >79.2 ng/mL had a relative risk of dying of 2.4 (P=0.013).

On the other hand, Engin et al. [27] found that concentrations of Ang-2 and Tie-2 were significantly higher in patients with GC than in controls, while concentrations of Ang-1 were not statistically different between the groups. Concentrations of Ang-1, Ang-2, and Tie-2 were not statistically different among the cancer stages. Jo et al. [28] reported that serum Ang-2 levels were higher in patients than in controls, and that the levels were strongly correlated with the presence of positive lymph nodes (P=0.008). Elevated Ang-2 levels and depth of tumor invasion were significant predictors of lymph node metastasis.

ANG-LIKE FAMILY

Yoshinaga et al. [29] studied Ang-like protein 2 (ANGPTL2), a protein that regulates angiogenesis, and reported that the expression and production of ANGPTL2 were both higher in undifferentiated cells (P<0.001 and P<0.050, respectively). Levels of ANGPTL2 in the serum of patients with GC were higher than those in healthy controls (P<0.010). Regarding angiogenic factors that were potential biomarkers for GC, only VEGF expression was confirmed in undifferentiated and differentiated cell lines. For the discrimination of patients with GC from individuals without cancer, the area under the curve for ANGPTL2 was 0.774 (P=0.005). Toiyama et al. [30] concluded that serum ANGPTL2 was significantly higher

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in patients with GC (P<0.050) and that its expression was associated with tumor progression, early recurrence (P=0.003), and poor prognosis (P=0.007).

INTERLEUKIN (IL) FAMILY

IL-12 is a cytokine produced by antigen-presenting cells with potent anti-tumor, anti-angiogenic, and anti-metastatic activities. IL-12 induces type 1 immune response and acts as a growth factor for T cells. VEGF inhibits the maturation of dendritic cells, which are the main source of IL-12 [31]. Nakayama et al. [32] concluded that IL-12-positive cell density significantly decreased in patients with carcinoembryonic antigen (CEA)-positive (P=0.037) or differentiated type (P=0.036) tumors. IL-12-positive cell density was not associated with serum levels, but tended to be inversely correlated with plasma levels of VEGF (P=0.080). Patients with GC with low IL-12-positive cell density or low serum levels of IL-12 might require additional immunochemotherapy after surgery [32].

Konno et al. [33] investigated IL-8, a cytokine with mitogenic activity. Plasma VEGF levels were higher in patients with GC, and even higher in patients with venous invasion. Peripheral levels of VEGF were correlated with the number (P=0.0064) and ratio (P=0.0058) of metastatic lymph nodes. IL-8 levels in drainage veins were related to both tumor site and lymph node metastases. Shorter disease-free survival was found to be associated with high IL-8 levels (>3.65 ng/mL), large tumors (>40 mm), deeply invasive tumors, lymph node involvement, and venous invasion.

STUDIES THAT COVER MULTIPLE FAMILIES

Blank et al. [34] studied several proteins. Lower VEGF and follistatin levels in serum were correlated with distant metastases (P=0.040 and P=0.002, respectively). Lower follistatin levels were also correlated with lymph node metastasis (P=0.031). Lower serum Ang-2 levels were correlated with lymph node metastasis (P=0.025). Higher serum VEGF levels were associated with positive lymph nodes (P=0.025). The VEGF levels (P=0.011) and the Ang-2/VEGF ratio (P=0.009) in the tissue were correlated with the extent of tumor regression. The Ang-2/VEGF ratio was also associated with clinical response (P=0.029), with a higher ratio in patients showing a positive response.

Park et al. [35] also studied a plethora of proteins, and showed higher VEGF-A levels in patients undergoing R1 resection compared with those undergoing R0 resection (P=0.037). Higher EGF levels were found in patients with poorly differentiated or undifferentiated tumors (P=0.020). Higher fibroblast growth factor 2 (FGF2) levels were observed in diffuse-type and undifferentiated tumors, as well as in extensive nodal disease (P=0.017, P=0.042, and P=0.046, respectively). OS was significantly worse in patients with higher levels of VEGF-A, hepatocyte growth factor (HGF), EGF, or FGF2. The VEGF-A level was a statistically significant independent prognostic factor for OS.

Gao et al. [36] documented that levels of CEA, cancer antigen (CA)-50, CA 19-9, laminin, and collagen type IV can be used as a parameter for metastasis and disease progression because their levels were significantly higher in patients with metastasis (P<0.050).

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HYPOXIA-INDUCIBLE FACTOR (HIF) FAMILY

HIF-1α is a critical transcription factor that activates the transcription of VEGF under hypoxic conditions and promotes tumor cell survival [37]. Hypoxia can also induce p53 that lacks its function and shows diminished apoptotic potential [38]. Oh et al. [39] demonstrated that p53 and HIF-1α were positively correlated with invasion depth (P=0.015 and P=0.001, respectively), and p53 and VEGF levels were correlated with lymph node involvement (P=0.040 and P=0.010, respectively). HIF-1α was observed to be a poor prognostic factor for disease recurrence or progression (P=0.002).

CONCLUSIONS

High levels of angiogenic and growth factors in serum and tumors are associated with worse outcomes in patients with gastric carcinomas. VEGF-A, the most extensively studied angiogenic factor, appears to be a useful biomarker for disease progression and remission, but not for diagnosis.

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