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Clinicopathological and Prognostic Outcomes of VEGF Expression in Resected Gastric Cancer Tissues. A Systematic Review

Brian Mawalla[1]
Xiaoxiao Luo[1]
Phillipo L. Chalya[2]
Xianglin Yuan[1]

[1]Department of Oncology Tongji Medical College, Wuhan, Hubei China
[2]Department of Surgery Bugando Medical Centre, Mwanza, Tanzania

Abstract

Background: Vascular endothelial growth factor VEGF families have been implicated in prognosis and clinicopathological outcomes in patients with gastric cancer. This review aims to assess the relationship of clinicopathological and prognostic outcomes of patients with gastric cancer, present with overexpression of VEGF families in gastric cancer tissues.

Methods: Full-published studies regarding clinicopathological and prognostic outcomes of patients with gastric cancer present with overexpression VEGF families sought through PubMed, MEDLINE, EMBASE and HINARI. The exclusion criteria for the reviewed literature were as follows. (1) The studies involved neoadjuvant or preoperative chemotherapy, chemoradiotherapy and target therapy. (2) Non-English articles. (3) The patients had multiple tumors. (4) The data sample was not reliable (5). The studies analyze the expression of VEGF in blood serum. STATA SE v. 13.1 (STATA_ Corporation, Texas, USA) has been used to analyze data. Statistical significant p-value was taken to be $P<0.05$ and two sided alpha of 5% implemented to determine confidence intervals and p-values. The outcomes of interest were clinicopathological and prognostic outcomes.

Results: In this review, 96 studies identified and left twelve eligible literatures to assess the clinicopathological and prognostic outcomes of VEGF expression in patients with gastric cancer. VEGF-A expression was found to be significantly associated with the size of the tumor ($P=0.028$), increase the risk of positive lymph nodes ($P=0.002$) and lymphovascular invasion ($P=0.001$). Also, it was found to be associated with poor prognosis for overall survival and disease-free survival in patients with gastric cancer. Studies have shown patients with high expression of VEGF-C protein had significantly poorer prognoses than a group with low VEGF-C expression. Also, expression of VEGF-C was evaluated, and it showed a substantial relation to TNM staging, vascular, and lymphatic invasion ($P<0.01$). The expression of VEGF-D in gastric cancer tissue correlated significantly with the size of the tumor, invasion to lymphatic and venous tissues and distant metastasis, all these contribute to the TNM stage, and it is useful in the evaluation of prognosis of gastric cancer patients regarding progression-free survival and overall survival.

Conclusion: This systematic review demonstrated that VEGF protein, especially VEGF-A, C and D overexpression in gastric cancer, all associated with poor prognosis and clinicopathological outcomes. We recommend that VEGF be a prognostic and predictive marker, and measured in all resected gastric cancer tissues to predict prognosis and clinicopathological outcomes of patients with gastric cancer.

Keywords

Gastric cancer; Clinicopathological; Prognosis outcome

Abbreviations

CI: Confidence Interval
GC: Gastric Cancer
TKIs: Tyrosine Kinase Inhibitors
HR: Hazard Ratio
OR: Odds Ratio
ORR: Overall Response Rate
OS: Overall Survival
PFS: Progression-free Survival
VEGFR: Vascular Endothelial Growth Factor Receptor
VEGF: Vascular Endothelial Growth Factor
EMBASE: Excerpta Medical Database
MEDLINE: Medical Literature Analysis and Retrieval System Online

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*Corresponding author:

Brian Mawalla
Department of Oncology
Tongji Medical College
Tongji Hospital
Huazhong University of Science and Technology
Wuhan, Hubei Province
China
Email: bsiza@yahoo.com

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Background

Global statistics of cancer diseases reported that gastric cancer is ranked the 5th common cancer and the 3rd common cause of deaths among patients with cancers [1]. This condition is predominant in males, with males to females ratio of 2:1 and the onset of the disease is commonly above 60 years [2]. For malignancies detected in early stages, a surgical procedure is the treatment of choice to cure the disease, but for those patients present with more advanced- stage malignancies, outcomes are poor [3]. The members of the VEGF family are five VEGF glycoproteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E) and placental growth factors 1, 2. VEGF families bind to vascular endothelial growth factors receptors such as VEGFR1 (Flt-1), VEGFR2 (Flk-1-KDR) and VEGFR3, which are expressed on the lymphatic and vascular endothelium; these are tyrosine kinase receptors. VEGF and its receptor are highly expressed in many malignancy types, including cancer found in the gastrointestinal tract. VEGF expression leads to the development and maintenance of a vascular network that promotes tumor growth and metastases. VEGF (A, B, C and D) are vascular endothelial growth factors families which have been implicated in the prognosis and clinicopathological picture of gastric cancer. VEGF families have been shown to cause neo-vascularisation, lymphangiogenesis, invasion depth of the tumor, metastasis, vascular invasion, and be associated with TNM staging. Studies have shown that metastasis and peritoneal dissemination are results of gastric cancer progression, and were the role-played by VEGF-A [4-6]. Some experimental studies have showed thatlymph node invasion is caused byVEGF-C and VEGF-D by acting as lymphangiogenic factors, enhancing lymphangiogenesis in tumors by binding to their specific receptors on the lymphatic tissues [7-10]. This review aims to assess the relationship of clinicopathological and prognostic outcomes of patients with gastric cancer, present with overexpression of VEGF families in gastric cancer tissues.

Methodology

Search strategy

HINARI, PubMed, EMBASE and MEDLINE were searched for the article written in English; the search started on October 16, 2016, and lasted until August 18, 2017. The strategies used to retrieve abstract and articles were as follows: [vascular endothelial growth factor] OR [VEGF]) AND [stomach OR gastric] AND ([cancer OR malignancy OR carcinoma OR tumor]) AND ([outcome]) AND prognosis AND clinicopathological features.

Study inclusion and exclusion criteria

The inclusion criteria mentioned were as follows below.

(1) The studies involving patients with resected gastric tumor (2) After resection, a sample of gastric cancer tissue taken for histopathological examination. (3) Over expression of VEGF was found in a gastric tumor. (4) The study reveals significant the relationship between clinicopathological parameters, prognosis features and VEGF expression levels. The exclusion criteria for the reviewed literature were as follows. (1) The studies involved neoadjuvant or preoperative chemotherapy, chemoradiotherapy and target therapy. (2) Non-English articles. (3) The patients had multiple tumors. (4) The data sample was not reliable (5) The studies analyze the expression of VEGF in blood serum.

Data collection and quality assessment

The review and data collection was conducted independently by two investigators (Brian Mawalla and Phillipo L Chalya). The consensus was sought to solve disagreements. The primary data obtained from the literature were first authors, gender, publication year, magnitude of the study, detailed histological classification, positive cases of VEGF, various stages of tumor (TNM), VEGFover expression in sample tissue, overall response rate (ORR), median progression-free survival (PFS), overall survival (OS) and their hazard ratio (HR). Qualities of studies methodology were assessed using Cochrane reviewer's criteria by reviewers BM and PLC independently.

Statistical data analysis

STATA SE v. 13.1 (STATA_ Corporation, Texas, USA) has been used to analyze data. Logistic regression and chi-square tests was used to identify the correlation between the level of the VEGF families' expression and the clinicopathological parameters. OS and PFS were calculated by using Kaplan-Meier method. Cox proportional hazards regression was used to calculate HR. Statistical significant p-value was taken to be $P<0.05$, and two sided alpha of 5% implemented to determine confidence intervals and p-values.

Results

Study selection

The primary search made 96 studies available for review, and reviewers chose 58 potential pieces of literature for full-text review. As many as 46 studies were excluded as they were found to have irrelevant information on the outcome of interest, this left 12 eligible studies for further review. Figure 1 shows a selection of the studies in this review.

Patient characteristics

2,089 patients were encompassed in this review. Gastric cancer tissues were taken surgically to detect VEGF strong expression in gastric tissues, and VEGF families' over expression in those tissues were detected by using immunohistochemical technique. 214 was the median number of patients, (ranges from 30 to 340). In this review, VEGF types (families) were studied in relation to prognosis and clinicopathological outcome.

Expression of VGEF families in gastric cancer tissue and its relationship to prognosis and clinicopathological outcomes

VEGF-A: Different studies investigate the VEGF-A detection in gastric tissues taken from patients with gastric cancer, and correlate with prognosis and clinicopathological outcome, one study showed that, the VEGF-A overexpression had unfavorable impact on DFS (HR = 1.85; 95% CI, 1.39–2.32) and (OS (HR = 1.57; 95% CI, 1.30–1.84) in gastric cancer patients; and this conclude that, VEGF-A expression shows a poor outcomes on OS and DFS in gastric cancer patients [11]. A positive significant association was seen between VEGF-A overexpression and TNM stage (P=0.047), and low VE GF-A expression was seen more in tumors with TNM stage I-II group (51.2%) compared to the group with TNM stage III-IV (48.8%), high VEGF-A expression (69.4%) was seen in-group of TNM stage III-IV compare to groupwith TNM stage I-II (30.6%); Furthermore, the VEGF-A strongexpression was observed to associate with the size of the tumor (P=0.028) and expression of VEGF-A was found to increase the risk of positive lymph nodes (P=0.002) and lymphovascular invasion (P=0.001) in gastric cancer patients [12]. Similar studies revealed that, VEGF-A strong expression was significant correlate with vascular invasions, formation of ascites, distant metastasis, haematogenous metastasis and tumor neo-vascularisation [13,14].

VEGF-B: There are limited studies that have been done to demonstrate the relationship between VEGF–B overexpression and clinicopathological outcomes. Research was done to quantify over-expression of VEGF-A and over-expression of VEGF-B, and results showed that VEGF-A tends to overexpress in gastro-esophageal cancers and correlates with tumor invasion, while VEGF-B does not seem to be involved in these tumors [14].

VEGF-C: The strongest relationship was revealed among VEGF-C over-expression with lymph node status, the invasion of venous tissues, invasion of lymphatic tissues and tumor-infiltrating patterns [15]. Related studies showed that patients with strong expression of VEGF-C presented with significantly poorer prognosis compared to those presented with low VEGF-C expression, and other similar studies showed poor prognoses in gastric cancer patients who presented with VEGF-C over-expression compared to those with low expression of VEGF-C [16,17]. A study done, and showed there was no association between depth of gastric cancer invasion, size of gastric

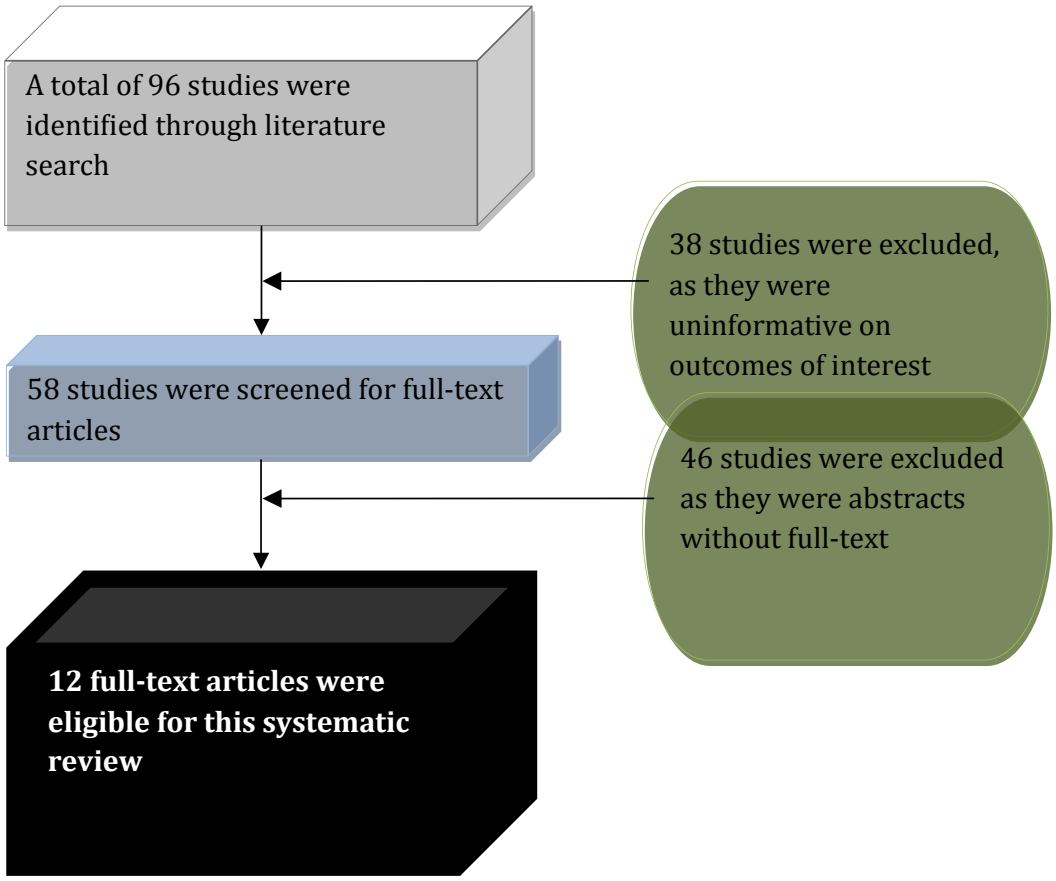

Figure 1: Flow diagram of the studies extracted in this review.

tumor, gender, age at time of surgery, tumor location and VEGF-C over-expression; although there was relationship between VEGF-C over-expression, TNM staging, vascular invasion and lymphatic invasion (P<0.01) [18].

Similar studies showed VEGF-C over-expression on tissue obtained from gastric cancer patients were positively associated with lymphatic system invasion (lymph tissues and lymph nodes invasion) [19-21]. Also, VEGF-C expression seen in early stage of gastric cancer was positive correlated with lymphatic invasion, and this could be hypothetically helpful to predict the effectiveness of less or more extensive surgical resections and lymph node clearance in patients with gastric cancer [20]. One study showed that gastric carcinoma (GC) exhibit high level of VEGF-C expression which was 54.90% compared to 35.29% in normal gastric tissues. The same study also showed that VEGF-C expression was significantly associated with less survival rates and lymph node metastasis in patients with GC [22].

VEGF-D: The study was done to elucidate the expression of VEGF-D in GC and it was found to be statistically significantly associated with lymphatic system invasion (lymphatic tissue and lymph node), depth of tumor invasion and tumor differentiation in early gastric cancer [22]. Also, evaluation of VEGF-D in other studies was found to correlate with the spread of tumor to lymphatic tissues, depth of tumor invasion and poor prognosis in colorectal, endometrial, ovarian, and breast cancer [23-28]. The presence VEGF-D in gastric tissues presented poor prognosis or unfavorable outcomes compared to the group with absence of VEGF-D expression in patients with gastric cancer, VEGF-D also used as a prognostic marker in patients with GC after surgical resection [22,29]. A study has shown that, the size of the tumor, distant metastasis and invasion of both lymphatic and venous tissues were significantly correlated with expression of VEGF-D; also VEGF-D can be used to evaluate RFS AND OS in patients with gastric cancer [30].

Discussion

2,089 patients were involved in this systematic review, and 12 eligible literatures were used to assess the clinicopathological and prognostic outcomes of VEGF's families expression in gastric cancer patients. Among known VEGF family, VEGF-A (VEGF) is the most common frequently studied subtype in gastric cancer [31]. Numerous studies have evaluated the importance of VEGF-A over expression as an independent prognostic marker in gastric cancer patients; however, these studies have shown conflicting results [32-35]. VEGF-A up-expression has been demonstrated in the recent meta-analysis as a poor prognosis factor in patients with gastric cancer regarding OS and DFS [11]. This systematic review used the Kaplan-Meier survival method to analyze the significant prognostic value of VEGF-A in GC. In gastric cancer,patients with high expression levels of VEGF-A showed poor prognosis compared to those with low expression levels of VEGF-A.

Different studies have demonstrated that there is no association between VEGF-B expression and prognosis outcomes; also VEGF-B expression and clinicopathological outcomes in gastric cancer patients [14,15]. One study, which analyzed the expression of both VEGF-A and VEGF-B showed that only VGEF-A was associated with prognosis and clinicopathological outcomes in patients with gastric carcinomas while no correlation was demonstrated in patients presented with the expression of VEGF-B [14].

The previous report has demonstrated that lymphatic system invasion (lymphatic tissue and lymph nodes) in gastric cancer was positive correlated with expression VEGF-C [16,17,21,22]. VEGF-C has been reported by Amioka et al. and Yanai et al. [21,37] as an important molecule in facilitating microvessel density and lymph node metastasis in gastric cancer, VEGF-C expression in GC was also found to associate with invasion of blood vessels [16,17].

Over expression of VEGF-D have been reported to have significant

association with poor prognosis, lymphatic metastases and decreased survival in patients with gastric cancer; however, those patients with absence of VEGF-D expression in their gastric tissues had a favorable prognosis [29]. Meta-analysis was done and suggested that over expression of VEGF-C and VEGF-D in gastric cancer was associated with poor prognosis [36].

Conclusion

This systematic review demonstrated that overexpression of VEGF proteins, especially VEGF-A, C and D, in gastric cancer is associated with poor prognosis and clinicopathological outcomes and therefore, may be used as a prognostic marker (for prediction of prognosis outcomes) and predictive marker (for evaluation of clinicopathological findings, (e.g., TNM stage, size tumor, invasion to the lymph nodes and invasion to the lymphovascular system) in gastric cancer patients. We recommend that VEGF be a biological marker, and to be measured in all resected gastric cancer tissues for prediction of prognosis and clinicopathological outcomes of gastric cancer patients.

Limitations

The inclusion of only Asian populations in the studies may have excluded some information present in studies in non -Asia population. (2) Exclusion of studies published in a language other than English may exclude information needed in this review.

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