The Correlation between Serum Vascular Endothelial Growth Factor (VEGF) Levels and Size of Colorectal Cancer Tumors

Eko A PANGARSA[1], C SUHARTI[1], D SANTOSA[1], Budi SETIAWAN[1], Aniq ULTHOFIAH[2]

1. *Division Haematology-Medical Oncology, Department of Medicine, School of Medicine, Diponegoro University, Kariadi Hospital, Semarang, Indonesia.*
2. *Department of Medicine, School of Medicine, Diponegoro University, Kariadi Hospital, Semarang, Indonesia.*

ABSTRACT

Background: Angiogenesis plays an important role in progression of colorectal carcinoma (CRC). Vascular endothelial growth factor (VEGF) is the predominant angiogenic factor in CRC and plays important role in cell mitosis, change in cell shape and increases vascular permeability. Vascular endothelial growth factor is expressed in approximately 50% of CRCs, and considered an important angiogenic factor in growth and development of CRC. In this study, we examined VEGF serum levels to asses corelation between serum VEGF levels and size of CRC tumors. **Patients and Methods:** This cross sectional study involved 17 CRC patients with stage I, II, III. who had undergone large bowel resection at Karyadi Hospital and had not chemotherapy. Size of tumors grading system according to TNM system based on abdominal CT, whether serum levels of VEGF was assessed by ELISA. **Results:** In this study, we found the grading tumor size T1, T2 and T3 was 23,5%, 29,4 % and 47,1 % respectively. Significant statistical correlation (p=0.001) was found between serum VEGF levels and size tumors of CRC with strong relationship (rho>0,7). **Conclusion:** This study showed a correlation between serum VEGF levels and size of colorectal cancer tumors. Whether VEGF levels is affected by surgical procedure, we need further study to evaluate serum VEGF levels before surgical and tumor size according to treatment response.

Keywords: *Angiogenesis, Colorectal Cancer, Tumor size, VEGF*

Colorectal cancer is the second most common cancer in the world. Colorectal cancer incidence rates is more prevalent in developed countries such as Australia, New Zealand, Canada and USA. In the United States, colorectal cancer is the second leading cause of death among those developed countries. In 2014, an estimated 136.830 people were diagnosed with colorectal cancer and 50.310 died. It is estimated that approximately 95270 new cases of large bowel cancer and 39220 new cases of colorectal cancer are diagnosed in 2016 [1-4].

Colorectal cancer is the abnormal growth of cells originates in the colon and the rectum. Colorectal cancer cells growth and development need vascularization to support food supply (angiogenesis) [5, 6].

Angiogenesis process is the formation of new blood vessels from the preexisting vasculature. Angiogenesis is a vital process in tumor growth and development and Vascular Endothelial Growth Factor (VEGF) is a potent stimulator in the angiogenic response [7].

VEGF contributes to tumor growth due to its capacity to induce blood vessels permeability (6).VEGF is the target of anticancer therapy because of its fundamental role in tumor growth [8]. Although tumor size remains a major prognostic value in many other solid organs cancer, its value in colon cancer may have long been neglected. In additional to our knowledge, the aim of this study is to determine the association of the serum Vascular Endothelial Growth Factor (VEGF) levels with tumor size in colorectal cancer.

METHODS

Sampels

Blood samples were taken from 17 colorectal cancer patients who had undergone large bowel resection at Karyadi Hospital. No patients had had previous malignant disease nor had received chemotherapy or radiotherapy. Blood samples were taken, at the time about 2 weeks after surgery.

Correspondence to: Eko A Pangarsa, MD, Division Haematology-Medical Oncology, Department of Medicine, School of Medicine, Diponegoro University , Kariadi Hospital, Semarang , Indonesia.
e-mail: hemasemarang@yahoo.com ,ekopangarsa90@gmail.com

Five cc blood was taken into a into serum separator tubes (SST) for serum analysis, and shaken to homogeneous. Wait for 30 -45 minutes until clothing. Samples were centrifuged at 3000 rpm for 15 minutes. The samples were stored at −20°C until assay by ELISA (Quantine R&D America). Using calibrator diluent RD5K, the minimum detectable dose of VEFG by ELISA is typically less than 5.0 pg/ml. All of the samples will sent with dryice to Prodia central laboratory in Jakarta.

All specimens were systematically reevaluated by expert pathologist in Karyadi hospital. Tumour staging was performed according to the TNM stage classification American Joint Committee on Cancer system 7th (2010) based on contrast abdominal CT.

Study Design

This was a cross-sectional study conducted over a period of 3 months at RSUP Dr. Kariadi Semarang, 17 patients were included. Correlation test was used to assess the association between the serum VEGF levels and tumor size in colorectal cancer.

Statistical Analysis

All collected data were tabulated and calculated using SPSS v.16, presented in numerical data, median and its variations.Spearman's rank test was used for the correlation analysis. A p-value <0.05 was considered statistically significant.

RESULTS

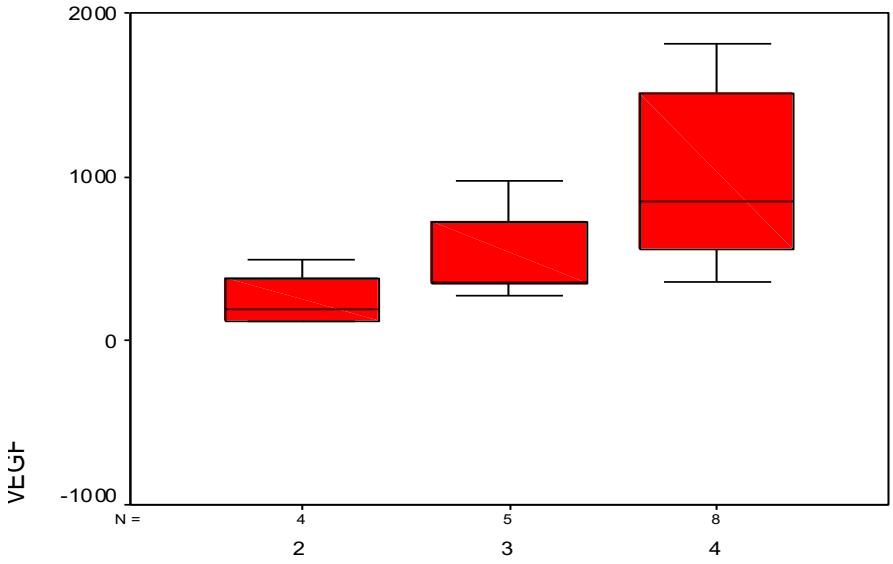
This study was conducted over a period of 3 months, a total of 17 samples were studied, consisted of 10 males (58,8%) and 7 females (41,2%). The age range of the subjects varied between 31 years and 81 years. According to age category, the subjects were divided into ≤ 50 years; 51-60 years; 61-70 years; 71-80 years; and >80 years with a count of 7(41,2%); 4(23,5%); 4(23,5%); 1 (5,9%), and 1(5,9%) respectively.

In this study we found tumor size of T4 in 8 subjects (47,1%), T3 in 5 subjects (29,41%), and T2 in 4 subjects (23,52%). Clinicopathologicalof samples are adenocarcinoma. Colorectal cancer stages of the subjects consisted of stages I to III who underwent surgery and never received chemotherapy All pertinent clinical and histopathological data of the patients are summarised in Table I.

Table1. Characteristics of the study population

Variables	N(%)	Mean ±SD	Median (Minimum-Maximum)
Gender			
Male	10 (58,8%)		
Female	7 (41,2%)		
Age (years)			
≤ 50 years	7 (41,2%)	53,71 ±13,959	
51-60 years	4 (23,5%)		
61-70 years	4 (23,5%)		
71-80 years	1 (5,9%)		
>80 years	1 (5,9%)		
Tumor size			
T2	4 (23,5%)		193 (120-494)
T3	5 (29,4%)		356 (276-973)
T4	8 (47,1%)		855 (357-1809)
Cancer stage			
I	2 (11,8%)	308 ± 263	
IIA	1 (5,9%)	729 ± 0	
IIC	1 (5,9%)	517 ± 0	
IIIA	2 (11,8%)	192 ± 101	
IIIB	10 (58,8%)	762 ± 479	
IIIC	1 (5,9%)	1809 ± 0	

This study found significant association between serum VEGF levels with tumor size in colorectal cancer P= 0,001 (P<0,05) with strong correlation (rho >0,7).



DISCUSSION

This study involved 17 colorectal cancer patients stages I, II, and III who underwent surgery and never received chemotherapy. Several studies have shown that colorectal cancer increases with age. Colorectal cancer is rare before the age of 40. The risk of developing colorectal cancer increases at the age of ≥50 years and becomes twice as large as in each subsequent decade. This study also found the that colorectal cancer rates washigher among the subjects who were older than 40 years compared to younger subjects, with the youngest participant of 31 years, and most of the study subjects were from the age of 40 - 60 years.

Vascular Endhotelial Growth Factor (VEGF) is endothelial cell-specific mitogen. VEGF is a mediator of angiogenesis that plays an important role in cell mitosis, cell shape alteration and increases vascular permeability.VEGF is involved in the growth and development of colorectal cancer. VEGF is correlated with the invasion of colorectal cancer cells, tumor vascular density, metastasis, tumor recurrence and poor prognosis, furthermore there is a strong association between colorectal cancer with apoptosis and angiogenesis [9]. Serum VEGF levels in the subjects of this study (mean 686,82 ± 516,729 pg/ml).

Large tumors may have independent prognostic significance as a result of several factors. Larger tumor size may also be a reflection of biologically more aggressive tumor. Although tumor size remains a major prognostic value in many other solid organs cancer, its value in colon cancer may have long been neglected [10]. In this study we found that tumor size of T4 in 8 subjects (47,1%), T3 in 5 subjects (29,41%), and T2 in 4 subjects (23,52%).

VEGF has an effect on the progressivity of colorectal cancer. According to several studies, increased levels of VEGF is associated with increased size of colorectal cancer tumors [10-12].

This study found significant association between serum VEGF levels with tumor size in colorectal cancer P= 0,001 (P<0,05) with strong correlation (rho >0,7). Increased VEGF tumor may be used as an independent prognostic parameters in the management of colorectal patients stages II and III [13-15]. Thisfinding is consistent with some previous studies. FerroniP, et al in 2005 reported that serum VEGF was associated with a large tumor (p = 0.005); another study by KemikOzgur et al, in 2011 found an association between serum VEGF levels and a large tumor with p = 0.0001, elevated serum VEGF levels was associated with the development of colorectal cancer. This finding is similar to the study conducted by Kwon et al's in 2010 with p = 0.012; Sahasukamal et al study in 2014 also revealed the correlation of high serum VEGF levels with increased tumor size, high serum VEGF levels was associated with poor prognosis

and larger tumor size decreased patient survival rate by 5 years [10, 11, 13, 15].

CONCLUSION

The present results demonstrate in This study has demonstratethat serum VEGF levels is significantly difference inassociated with tumor size in colorectal cancerinpreviously untreated colorectal cancer patients who never received chemotherapy. High level VEGF serum associate with the larger the tumor. Surgical procedures may affect VEGF levels, so further studies are may needed to assess the effect of surgery to VEGF alterations. VEGF seems to be an indicator of poor prognosis, as well was correlated with tumour size, further studies needed to see association between VEGF levels with less favourable long-term survival.

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Lab Prodia Jakarta, Indonesia

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