

Serum Vascular Endothelial Growth Factor (VEGF) and Microvessel Tumor Invasion in Hepatocellular Carcinomas

Seong Woo Hong, M.D., Dong Hee Whang, M.D.¹, In Wook Paik, M.D. and Hyuck Sang Lee, M.D.

Purpose: Vascular endothelial growth factor (VEGF) is a potent angiogenic factor in a number of cancers. The aim of this study was to evaluate the clinical significance of the serum level of VEGF in hepatocellular carcinoma (HCC) patients.

Methods: Serum VEGF was measured by an enzyme linked immunosorbent assay (ELISA) method. The correlation between serum VEGF level and clinico-pathological data of HCC patients were evaluated.

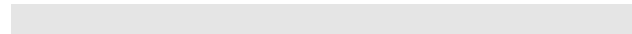
Results: The serum VEGF levels significantly increased with increasing tumor size and platelets count. The mean serum VEGF level in HCC patients with microvessel tumor invasion was higher than in those without microvessel tumor invasion.

Conclusion: A high serum VEGF level may be an indicator of tumor progression and an important predictor of microvessel tumor invasion. (J Korean Surg Soc 2003;64: 224-228)

Key Words: Vascular endothelial growth factor, Hepatocellular carcinoma, Microvessel tumor invasion

Departments of Surgery and ¹Laboratory Medicine, Inje University, Seoul Paik Hospital, Seoul, Korea

: 2가 85
Ⓢ 100-032,
Tel: 02-2270-0016, Fax: 02-2270-0373
E-mail: lib0196@thrunet.com
: 2002 11 15 , : 2002 12 20
1999



가
가
(1) 가 (Vascular Endothelial Growth Factor, VEGF)
(2) , VEGF ,
(3-6) , VEGF
1994 Kondo (7) ELISA (Enzyme linked immunosorbent assay)
(8-11)
가
VEGF 가
(12-15)
VEGF
VEGF



ELISA kit (Quantikine human VEGF, R&D systems, Mineapolis, U.S.A.)
 -70°C 가
 VEGF
 quantitative sandwich enzyme immunoassay, microwell plate VEGF enzyme
 VEGF
 enzyme
 VEGF 450 nm
 microplate readers (Emax, Molecular Devices Corporation, California, U.S.A.)
 9.0 pg/ml
 VEGF
 10
 VEGF

Table 1. Clinical factor and serum level of VEGF in hepatocellular carconoma patients

Factor	Stratification	No. of patients	VEGF*	P-value
Gender	Male	21	237.8±159.5	0.194
	Female	7	474.0±454.8	
Age (years)	< 55	12	501.3±532.5	0.346
	55	16	350.2±295.1	
HBsAg	Negative	9	302.6±339.6	0.385
	Positive	18	452.7±447.8	
Anti-HCV Ab	Negative	21	466.6±446.8	0.299
	Positive	6	261.5±270.4	
Albumin	3.5 gm/dl	7	552.8±633.6	0.209
	> 3.5 gm/dl	20	350.1±311.7	
ICG R ₁₅ †	10%	10	272.5±200.5	0.685
	> 10%	13	371.8±328.9	
PVT ‡	Absence	18	308.4±213.4	0.158
	Presence	10	606.8±599.2	
No. of tumor	1	12	320.5±267.4	0.352
	2	14	487.1±526.7	
Cirrhosis	Absence	4	247.5±188.2	0.382
	Presence	23	450.4±442.8	
TNM stage	I, II	10	299.8±251.2	0.253
	III, IV	18	478.9±473.2	
Distant Metastasis	Absence	25	381.4±416.8	0.220
	Presence	3	694.4±274.3	

*VEGF = serum level of vascular endothelial growth factor (pg/ml), mean±standard deviation; † ICG R₁₅ = indocyanine green 15 minutes retention rate; ‡ PVT = portal vein thrombosis.
 SPSS

0.05

1) VEGF
 28 54.4 , 가
 21 가 7 . B (HBsAg)
 가 17 (65.4%), C (anti-HCV Ab)가
 가 5 (19.2%) 가 4
 (15.4%)
 가 23 85.2%
 VEGF 415.0±412.0 pg/ml
 16.6 pg/ml, 1948.0 pg/ml 373.1 pg/ml
 , HBsAg, anti-HCV Ab, , ICG
 R15 (indocyanine green 15),
 , TNM VEGF 가 (Table 1).

VEGF 606.8 pg/ml
 VEGF 308.4 pg/ml (P=0.158)
 , VEGF 800 pg/ml
 4 , VEGF
 가 500 pg/ml 7 5 (71.4%) 가
 (23.8%) , 500 pg/ml 21 5
 가 (P=0.063).
 VEGF
 Pearson correlation
 VEGF r=0.577 가
 (P=0.001)(Fig. 1).
 r=0.486
 (P=0.01)(Fig. 2).

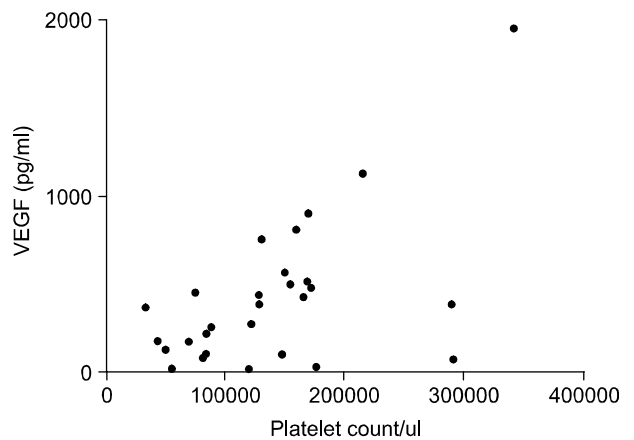


Fig. 1. Correlation of serum VEGF (Vascular endothelial growth factor, pg/ml) level with platelet counts (r=0.577, P=0.001).

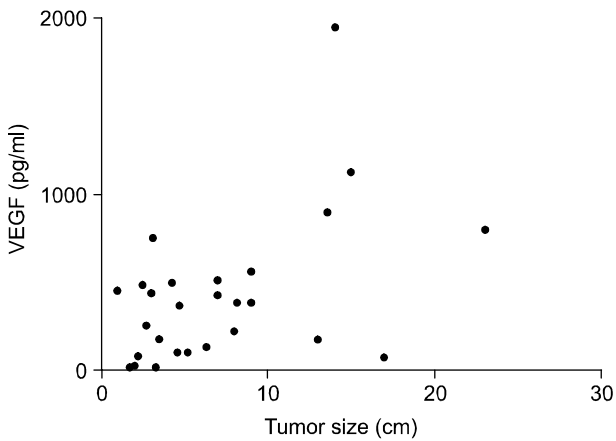


Fig. 2. Correlation of serum VEGF (Vascular endothelial growth factor, pg/ml) level with tumor size (cm) ($r=0.486$, $P=0.01$).

Table 2. Pathological factor and serum level of VEGF in resected hepatocellular carcinoma patients

Factor	Stratification	No. of patients	VEGF*	P-value
Size of tumor	5 cm	5	122.5±201.5	0.129
	> 5 cm	5	332.4±190.2	
No. of tumor	1	7	250.7±209.5	0.632
	2	3	173.3±265.8	
IM [†]	Absence	6	181.2±212.5	0.385
	Presence	4	296.9±230.4	
Microvessel invasion	Absence	4	33.1±28.8	0.006
	Presence	6	357.0±180.5	
TNM stage	I, II	4	220.4±228.3	0.908
	III, IV	6	238.1±228.0	
ES [‡] grade	I	4	134.4±195.4	0.290
	II, III	6	289.5±221.3	
Cirrhosis	Absence	2	227.8±219.1	0.999
	Presence	8	227.4±229.6	

*VEGF = serum level of vascular endothelial growth factor (pg/ml), mean±standard deviation; [†] IM = intrahepatic metastasis; [‡] ES = edmondson-Steiner grade.

2) VEGF 가 가 10 VEGF (), , TNM , Edmondson-Steiner grade, VEGF 357.0 pg/ml 33.1 pg/ml (P=0.006)(Table 2). VEGF가 370 pg/ml 4

VEGF 가 2~3 mm 가 (Vascular Endothelial Growth Factor, VEGF) (1) 가 (3-6) VEGF 가 Kondo (7) enzyme-linked immunosorbent assay (ELISA) VEGF 가 VEGF가 Kumar (9) VEGF 가 가 VEGF 가 가 VEGF (16,17) Jinno (13) VEGF 가 가 VEGF가 가 (18) VEGF , VEGF VEGF가 VEGF 가 VEGF가 800 pg/ml 500 (P=0.063) 가 가 ,

VEGF

VEGF가

가

(19)

4.4 가 가

(20)

(21) Poon (22)

VEGF (500 pg/ml)

(5 cm)가 가

가

VEGF (18)

VEGF

(23)

VEGF

(24)

가

가

VEGF가

REFERENCES

- 1) Folkman J, Shing Y. Angiogenesis. *J Biol Chem* 1992;267:10931-4.
- 2) Zimmerman M, Selzman CH, Harken AH. Surgical implications of therapeutic angiogenesis. *Surgery* 1999;125:243-9.
- 3) Brown LF, Berse B, Jackman RW, Tognazzi K, Manseau EJ, Senger DR, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. *Cancer Res* 1993;53:4727-35.
- 4) Saito H, Tsujitani S, Kondo A, Ikeguchi M, Maeta M, Kaibara N. Expression of vascular endothelial growth factor correlates with hematogenous recurrence in gastric carcinoma. *Surgery* 1999;125:195-201.
- 5) Takahashi Y, Bucana CD, Cleary KR, Ellis LM. p53, vessel count and vascular endothelial growth factor expression in human colon cancer. *Int J Cancer* 1998;79:34-8.
- 6) Hartenbach EM, Olson TA, Goswitz JJ, Mohanaraj D, Twigg LB, Carson LF, et al. Vascular endothelial growth factor (VEGF) expression and survival in human epithelial ovarian carcinomas. *Cancer Letters* 1997;121:169-75.
- 7) Kondo S, Asano M, Matsuo K, Ohmori I, Suzuki H. Vascular endothelial growth factor/vascular permeability factor is detectable in the sera of tumor-bearing mice and cancer patients. *Biochem Biophys Acta* 1994;1221:211-4.
- 8) Yamamoto Y, Toi M, Kondo S, Matsumoto T, Suzuki H, Kitamura M, et al. Concentration of vascular endothelial growth factor in the sera of normal controls and cancer patients. *Clin Cancer Res* 1996;2:821-6.
- 9) Kumar H, Heer K, Lee PWR, Duthie GS, MacDonald AW, Greenman J, et al. Preoperative serum vascular endothelial growth factor can predict stage in colorectal cancer. *Clin Cancer Res* 1998;4:1279-85.
- 10) Obemair A, Tempfer C, Hefler L, Preyer O, Kaider A, Zeillinger R, et al. Concentration of vascular endothelial growth factor (VEGF) in the serum of patients with suspected ovarian cancer. *Br J Cancer* 1998;77:1870-4.
- 11) Dirix LY, Vermeulen PB, Pawinski A, Prove A, Benoy I, Pooter CD, et al. Elevated levels of the angiogenic cytokines basic fibroblast growth factor and vascular endothelial growth factor in sera of cancer patients. *Br J Cancer* 1997;76:238-43.
- 12) Fang Y, Hu M, Liu K. Kinetics of tumorigenic vascular endothelial growth factor signalling and its significance in human hepatocellular carcinoma cells. *Biomed Pharmacothera* 2001;55:102-10.
- 13) Jinno K, Tanimizu M, Hyodo I, Nishikawa Y, Hosokawa Y, Doi T, et al. Circulating vascular endothelial growth factor (VEGF) is a possible tumor marker for metastasis in human hepatocellular carcinoma. *J Gastroenterol* 1998;33:376-82.
- 14) Shimamura T, Saito S, Morita K, Kitamura T, Morimoto M, Kiba T, et al. Hepatocellular carcinoma and vascular endothelial growth factor receptors. *J Gastroenterol Hepato* 2000;15:640-6.
- 15) Ng IOL, Poon RTP, Lee JMF, Fan ST, Ng M, Tso WK. Microvessel density, vascular endothelial growth factor and its receptors Flt-1 and Flk-1/KDR in hepatocellular carcinoma. *Am J Clin Pathol* 2001;116:838-45.
- 16) Park YN, Kim YB, Yang KM, Park CI. Increased expression of vascular endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis. *Arch Pathol Lab Med* 2000;124:1061-5.
- 17) Suzuki K, Hayashi N, Miyamoto Y, Yamamoto M, Ohkawa K, Ito Y, et al. Expression of vascular permeability factor/vascular endothelial growth factor in human hepatocellular carcinoma. *Cancer Res* 1996;56:3004-9.
- 18) Jo YH, Hong SW, Yu JH, Um TH, Nah YW, Lee HS. Serum vascular endothelial growth factor in hepatocellular carcinoma. *Kor J HBP Surg* 2000;4:7-12.
- 19) Nagasue N, Ono T, Yamanoi A, Kohno H, El-Assal ON, Taniura H, et al. Prognostic factors and survival after hepatic

- resection for hepatocellular carcinoma without cirrhosis. *Br J Surg* 2001;88:515-22.
- 20) Iwatsuki S, Dvorchick I, Marsh JW, Madariaga JR, Carr B, Fung JJ, et al. Liver transplantation for hepatocellular carcinoma: A proposal of a prognostic scoring system. *J Am Coll Surg* 2000;191:389-94.
- 21) Esnaola NF, Lauwers GY, Mirza NQ, Nagorny DM, Doherty D, Ikai I, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg* 2001;6:224-32.
- 22) Poon RT, Ng IO, Lau C, Zhu LX, Yu WC, Lo CM, et al. Serum vascular endothelial growth factor predicts venous invasion in hepatocellular carcinoma: a prospective study. *Ann Surg* 2001;233:227-35.
- 23) Vermeulen PB, Salven P, Benoy I, Gasparini G, Dirix LY. Blood platelets and serum VEGF in cancer patients. *Br J Cancer* 1999;79:370-1.
- 24) Pinedo HM, Verheul HMW, D'Amato RJ, Folkman J. Involvement of platelets in tumour angiogenesis? *Lancet* 1998;352:1775-7.
-