

The Diagnostic Value of Serum Vascular Endothelial Growth Factor as a Predictor of Hepatocellular Carcinoma in Patients with HCV related Liver Cirrhosis

Thesis

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List of Abbreviations

AAT	Alpha-1 Antitrypsin
ACS	Anorexia-cachexia syndrome
AFP	Alfa feto protien
AFP-L3	Alpha-fetoprotein Lens culinaris agglutiin 3
AFU	α -l-fucosidase
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferas.
Ang2	Angiopoietin-2
ARE	Antioxidant Response Element
AST	Aspartate aminotransferase
BCL-2	B-cell lymphoma 2
BCLC	Barcelona Clinic Liver Cancer
CEPs	Circulating bone marrow-derived endothelial precursor cells
CLIP	Cancer of Liver Italian Program
CT	Computed tomography.
CUI	Chinese University Prognostic Index
DCP	Des gamma carboxy prothrombin
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
EUS	Endoscopic ultra sonography
FLK-1	Fetal liver kinase
FLT-1	Fms-like tyrosine kinase
GDP	Guanosine 5'-diphosphate

List of Abbreviations (Cont.)

GGT	Gamma-glutamyl transpeptidase
GP73	Golgi protein 73
GPC3	Glypican-3
GPI	Glycosyl phosphatidyl inositol
HBe Ag	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen.
HBV	Hepatitis b virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis c virus
HIF	Hypoxia-inducible factor
HIV	Human immune deficiency virus
HSC	Hepatic stellate cell
HSP	Heat shock protien
HTA gene	Hepatoma-associated gene
hTERT	Human telomerase reverse transcriptase
ICC	Cholangiocarcinoma
IFN	Interferon
IFP	Interstitial fluid pressure
IL-1	Interlukin-1
INH	Isoniazid
INR	International normalized ratio
IOUS	Intra operative ultrasonography
JIS	Japan Integrated Staging score
KDR	Kinase insert domain receptor
LFT	Liver function tests

List of Abbreviations (Cont.)

MAP Kinase	Mitogen activated protien kinase
MEK	Mitgen-activated protein kinase
MELD	Model for endstage liver disease
MHC-1	Major histocompatibility complex class 1
miRNA	micro RNA
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance imaging.
m-RNA	Messenger RNA
MSCT	Multi-Slice CT
M-TOR	Mammalian target of rapamycin
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NF-κB	Nuclear factor kappa-light-chain- enhancer of activated B cells
NK cells	Natural killer cells
NRF	Nuclear factor erythroid related factor
PAF	Platelet activating factor
PAI	Percutaneous Acetic Acid Injection
PAT	Parenteral anti Schistosomal therapy
PBC	Primary biliary cirrhosis
PDGF	Platelet derived growth factor
PEI	Percutaneous Ethanol Injection
PENT pathway	Pentose phosphate pathway
PGA	Gamma-glutamyl transpeptidase activity, and serum apolipoprotein A1 concentration index

List of Abbreviations (Cont.)

PI3K	Phosphoinositide 3-kinase
PIVKA II	Prothrombin induced by Vitamin K Absence II
PLGF	Placental growth factor
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PUO	Pyrexia of unknown origin
PVT	Portal vein thrombosis
PZQ	Praziquantel
RAF-1	Rapidly Accelerated Fibrosarcoma
RCC	Renal cell cancer
RFA	Radiofrequency ablation.
ROS	Called reactive oxygen species
ROS	Reactive oxygen species
SCCA	Squamous cell carcinoma antigen
SCCA-IgM IC	Squamous cell carcinoma antigen- immunoglobulin M immune complex
TAC	Trans arterial chemotherapy
TACE	Transarterial chemoembolization
TAE	trans arterial embolization
TAG-72	Tumor associated glycoprotein
TE	Transient elastography
TGF	Transforming growth factor
TIMPs	Tissue inhibitors of metalloproteinases
TKI	Tyrosine kinase inhibitor

List of Abbreviations (Cont.)

TKR	Tyrosine kinase receptor
TLR4	Toll-like receptor -4
TLS	Tuomr lysis syndrome
TNF	Tumour necrosis factor
TNM	Tumor-node-metastasis
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
US	Ultrasonography
VEGF	Vascular endothelial growth factor
VEGF	Vascular Endothelial Growth Factor Receptors
Vil1	Villin1
ZAG	Zinc alfa 2 glycoprotien

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is considered one of the major causes of end-stage liver disease including cirrhosis and hepatocellular carcinoma. HCV infects more than 170 million people worldwide (*Nelson et al., 2011*).

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and is associated with the second lowest 5-year survival rate of all tumor types. Despite some advances in early diagnosis and therapeutic strategies, HCC prognosis remains poor. Therefore, the identification of a novel marker correlating with the clinic pathological features and prognosis is highly desirable (*Jemal et al., 2010*).

Long as HCC most commonly appears in a patient with chronic viral hepatitis (hepatitis B or hepatitis C, 20%) or/and with cirrhosis (about 80%). These patients commonly undergo surveillance with ultrasound due to the cost-effectiveness. In patients with a higher suspicion of HCC (such as rising alpha-fetoprotein and des-gamma carboxyprothrombin levels), the best method of diagnosis involves a Triphasic CT scan of the abdomen using intravenous contrast agent and three-phase scanning (before contrast administration, immediately after contrast administration, and again after a delay) with the key characteristics on CT which are hypervascularity in the arterial

phase scans, washout or de-enhancement in the portal and delayed phase studies. A biopsy is not needed to confirm the diagnosis of HCC if certain imaging criteria are met (*Kaido et al., 2011*).

An alternative to a CT imaging study would be the MRI. MRI's are more expensive and not as available because fewer facilities have MRI machines. More important MRI are just beginning to be used in tumor detection and fewer radiologists are skilled at finding tumors with MRI studies when it is used as a screening device. Mostly the radiologists are using MRIs to do a secondary study to look at an area where a tumor has already been detected. MRI's also use contrast agents. One of the best for showing details of liver tumors is very new: iron oxide nano-particles appears to give better results. The latter are absorbed by normal liver tissue, but not tumors or scar tissue (*Tanaka et al., 2012*).

Several studies have also suggested a relationship between the progression of chronic liver disease and hepatocarcinogenesis. Chronic inflammation in the cirrhotic liver induces architectural and functional changes that result in hypoxia, one of the most potent stimuli for angiogenesis. Angiogenesis is essential for carcinogenesis and is induced directly by vascular endothelial growth factor (VEGF), leading to tumor growth and metastasis (*Wu, 2006*).

VEGF is a primary driving force for both physiological and pathological angiogenesis. VEGF expression is correlated with tumor vascularity (*Semela and Dufour, 2005*).

The vascular endothelial growth factor gene family, which encodes five polypeptide growth factors, VEGF-A, -B, -C, -D, and placenta like growth factor (PLGF), is particularly important because of its angiogenic and lymphangiogenic properties that promote the growth and metastasis of neoplasms. VEGF-C is regarded as the most efficient factor in regulating lymph angiogenesis (*Li et al., 2011*).