Diagnostic and Prognostic Value of Alpha-L-fucosidase as a Tumor Marker of HCC in Egyptian Patients

Thesis submitted for partial fulfillment of
Master degree in Tropical Medicine

By

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M.B., B.cH

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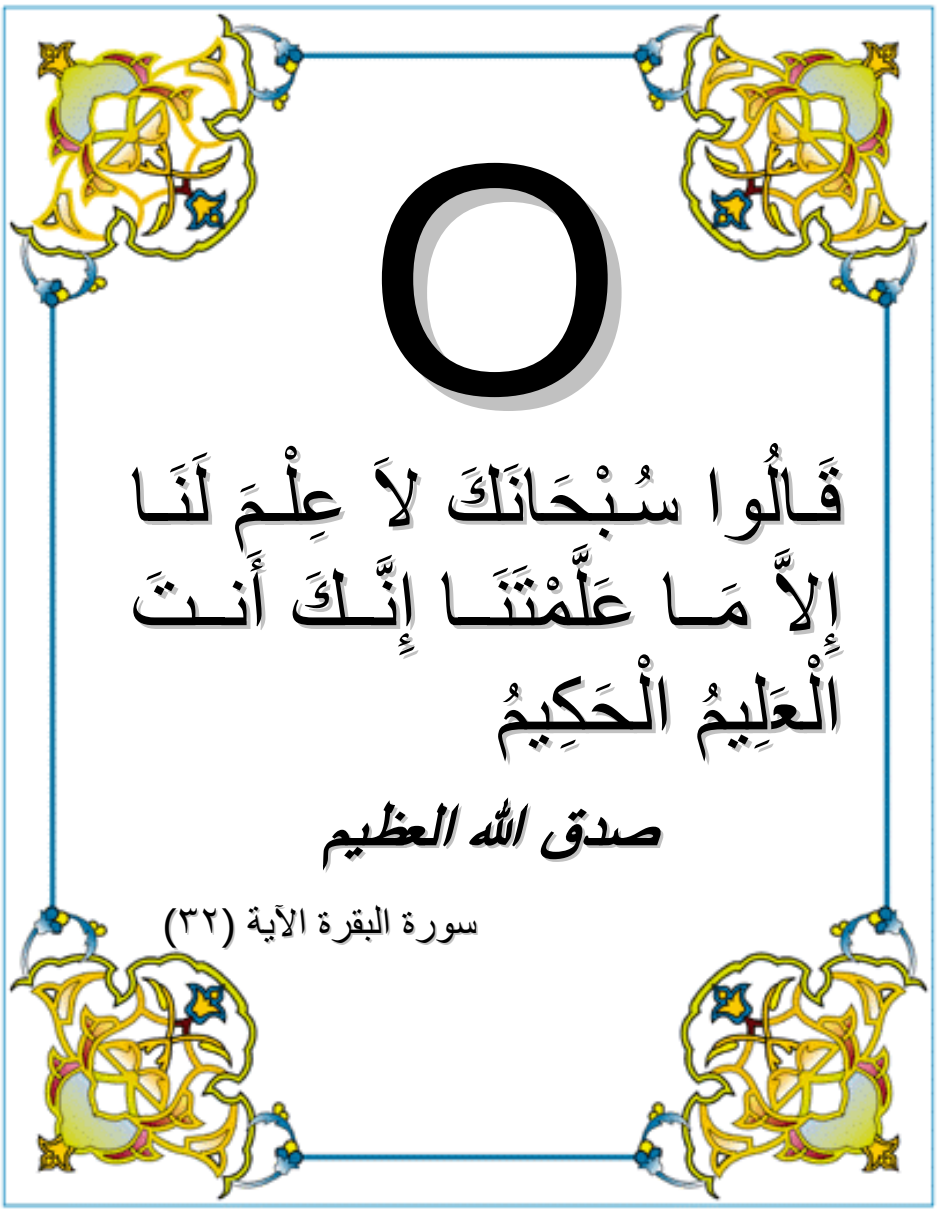

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قَـالُوا سُـبْحَانَكَ لاَ عِلْـمَ لَنَـا
إِلاَّ مَـا عَلَّمْتَنَـا إِنَّـكَ أَنـتَ
الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

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List of abbreviations

AASLD	American Association for the study of the liver disease
AAT	Alpha-1-antitrypsin
Ad	Adenoviral
AFB1	Aflatoxin B1
AFP	Alpha-fetoprotein
AFPIC	Alpha-fetoprotein immunocomplexes
AFP L3	Lens culinaris agglutinin reactive alpha fetoprotein
AFU	Alpha-L-fucosidase
AJCC	The American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	Analysis of Variance
AST	Aspartate transaminase
BCLC System	The Barcelona-Clinic- Liver-Cancer system
BCS	Budd-Chiari syndrome
BSA	Bovine Serum Albumin
CD	cytosine deaminase
CECT	Contrast enhanced helical computed tomography
CEUS	Contrast enhanced ultrasound
CgA	Chromogranin-A
CLD	Chronic liver disease
CLIP	The Cancer of the Liver Italian Program
CT	Computed tomography
CTAP	CT arterial portography
CTHA	CT during hepatic arteriography
CUPI	Chinese University Prognostic Index
DCP	Des-gamma carboxyprothrombin
DGCP	Des-γ-carboxy prothrombin
DNA	Dinucleic acid
DPR	The differential positive rate curve
EASL	European association for the study of the

	liver
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
5-FC	5-.fluorocytosine
FDA	Food and Drug Administration
FLR	Future liver remnant
FNAB	Fine needle aspiration biopsy
5-FU	5-fluorouracil
GCV	Ganciclovir
GGT	Gamma-glutamyl transpeptidase
GP73	Golgi protein 73
GPC3	Glypican-3
G6P	Glucose-6-phosphatase
H-ALP	HCC Specific Alkaline Phosphatase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFL	Hepatic focal lesion
HGF	Hepatocyte growth factor
HIFU	High intensity focused ultrasound
HMG CoA reductase	Hydroxy methyl glutaryl coenzyme A reductase
HS-GGT	Hepatoma-specific GGT
HSP	Heat shock protein
HSV	Herpes Simplex virus
HSV-tk	Herpes simplex virus thymidine kinase
hTERT	Human telomerase reverse transcriptase
HTN	Hypertension
^{131}I	Iodine-131
ICG	Indocyanine Green
ICG R15(%)	Indocyanine Green retention rate at 15 minutes
IGF-II	Insulin like growth factor- II
ILP	Interstitial laser photocoagulation
IL-8	Interleukin-8
INR	International normalized ratio

IVC	Inferior vena cava
JIS Score	The Japan Integrated Staging score
LCA	Lens culinaris agglutinin
LCSGJ	The Liver Cancer Study Group of Japan
LDH	Lactate dehydrogenase
LITT	Laser induced thermotherapy
LT	Liver Transplantation
MAA	Macro-aggregated albumin
MCT	Microwave Coagulation Therapy
MDCT	Multidetector helical CT
MELD	The Model for End Stage Liver Disease
mJIS	The modified Japan Integrated Staging
MOVC	Membranous obstruction of the inferior vena cava
MPCT	Multiphasic helical CT
MRI	Magnetic resonance imaging
mRNA	Massenger Ribonucleic acid
NASH	Nonalcoholic steatohepatitis
5`-NPD	5`-Nucleotide phosphodiesterase
OLT	Orthotopic liver transplantation
PAS	Periodic acid–Schiff
PAT	Parenteral anti-schistosomal treatment
PBC	Primary biliary cirrhosis
PBMCs	Peripheral blood mononuclear cells
PCT	Porphyria cutanea tarda
PDGFR	Platelet derived growth factor receptor
PEI	Percutaneous ethanol injection
PEIT	Percutaneous ethanol injection treatment
PIAF	Cisplatin/Interferon a2b/Doxorrubicin/Fluorouracil
PIVKA-II	Protein induced by vitamin K absence or antagonist II
PMCT	Percutaneous Microwave Coagulation
PS	The performance status score
PSC	Primary sclerosing Cholangitis
PSI	Percutaneous hot saline injection

PUO	Pyrexia of unknown origin
PVE	Portal vein embolism
PVT	Portal vein thrombosis
RCT	Randomized Controlled Trial
RFA	Radiofrequency ablation
RILD	Radiation induced liver disease
ROC	The receiver operating characteristic curve
RT-PCR	Reverse transcription polymerase chain reaction
SBP	spontaneous bacterial peritonitis
SCCA	Serum squamous cell carcinoma antigen
SCCAIC	Serum squamous cell carcinoma antigen immunocomplexes
SD	Standard Deviation
SELDI-TOF	Surface-enhanced laser desorption/ionization-time of flight mass spectrometry
sGPC3	soluble Glypican-3
SIRT	Selective internal radiation therapy
TACE	Transarterial chemoembolization
TGF-α	Transforming growth factor-α
TGF-β1	Transforming Growth Factor-beta 1
TNM Staging System	Tumor, Node and Metastases Staging System
UNOS	United Network of Organ Sharing
US	Ultrasonography
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VSV	Vesicular Stomatitis virus
WHO	World Health Organization

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world and the third most common cause of cancer related death ***(Llovet et al., 2003)***. It causes an estimated 1,2500,00 deaths every year worldwide ***(Globocan, 2000 and Bazarbashi, 2000)***. HCC constitutes 7.5% of all cancer types in males and is the 5th most frequent cancer site for males after lung, prostate, stomach and colorectal cancer. For females, it is the 8th most common, accounting for 3.5% of all cancer types. Its incidence is increasing worldwide ranging between 3% and 9% annually ***(Velazquez et al., 2003)***.

Hepatitis B (HBV) or C virus (HCV) chronic infections account for 75% of HCCs whereas nonviral etiologies as alcohol, genetic or metabolic disorders represent less than 25% of cases ***(Llovet et al., 2003)***. Furthermore, western countries suffer from a substantial and constant increase of HCC incidence due to HCV infection. Dramatically, HCC is a poor prognosis tumor, and is the first cause of death in cirrhotic patients. Current therapies are rather inefficient, mainly due to late diagnosis in usual and high recurrence rates within the remaining cirrhotic liver after surgical resection ***(El-Serag et al., 2003)***. Therefore, early detection is important in the management of this type of cancer.

Surveillance programs have been conducted in many countries to detect HCC at an early stage. Alpha fetoprotein (AFP) and ultrasonography are usually used as diagnostic tools ***(Giardina et al., 1998)***. However, not all HCC secrete AFP and AFP levels may be normal in as many as 40% of patients with

early HCC ***(Pateron et al., 1994)***. Ultrasonography is very effective in the early diagnosis of HCC and because of its improved performance, HCC was detected in 76% of HCC cases in a surveillance program ***(Zoli et al., 1972)***. However, ultrasonographic findings sometimes are not specific ***(Mayes, 2000)*** and contrasting data have been reported in the past regarding the utility of ultrasonography in the diagnosis of HCC at an early stage, even when performed together with serum AFP level determination. Therefore, more sensitive diagnostic tools for detecting HCC are desirable, particularly in the screening of cirrhotic patients, because it has been suggested that the disease may respond more favorably to treatment at an early stage ***(Pateron et al., 1994)***.

Tumor markers are potential screening tools that are widely used for early diagnosis of tumors ***(Elshemey et al., 2003)***. Many research groups are evaluating the sensitivity of available tumor markers and also are investigating the development of novel markers. The primary marker for HCC is α-fetoprotein (AFP), a single polypeptide chain glycoprotein. Generally, AFP shows acceptable sensitivity; however, AFP is not secreted in all cases of HCC and may be normal in as many as 40% of patients with early HCC ***(Nakatsura et al., 2003)***.

Among other HCC tumor markers is α-L-fucosidase (AFU), a lysosomal enzyme present in all mammalian cells. AFU has been proposed as a tumor marker since many studies reported increased AFU serum levels in patients with cirrhosis and HCC ***(Giardina et al., 1998)***. However, it is not correlated to AFP level in serum ***(Tangkijvanich et al., 1999)***.