ROLE OF GLYPICAN-3 IN DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

Thesis

Submitted for Fulfillment of the Master's Degree in Tropical Medicine

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رسالة

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مقدمة من الطبيب

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SUMMARY

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality after lung and stomach cancers ***(Al Knawy et al., 2009).*** In Egypt, the annual proportion of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002 ***(El-Zayadi et al., 2005).***

The aim of this study was to evaluate the diagnostic value of Glypican 3 as a tumor marker of HCC.

This study was conducted on 90 persons who were divided into three groups:

Group I (HCC group); included 30 patients with HCC on the background of liver cirrhosis. Thire ages ranged between 47-65year (median=54.00)**.**

Group II (chronic liver disease group); included 30 patients with chronic liver disease without any evidence of hepatic focal lesions as excluded by ultrasonography and AFP estimation. Diagnosis of chronic liver disease was based on standard clinical, biochemical, ultrasonographic criteria and pathological data whenever feasible. Thire ages ranged between 45-61 years (median=51.50).

Group III included 30 normal subjects who served as the control group.

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Ismail Mohamed Abdulsamea

بسم الله الرحمن الرحيم

﴿ وَأَنْزَلَ اللهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا ﴾

صدق الله العظيم

سورة النساء آية (١١٣)

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List of Abbreviations

AASLD	American Association for the study of the liver disease
AFB1	Aflatoxin B1
AFP.....	Alpha-fetoprotein
AFP L3	Lens culinaris agglutinin reactive alpha fetoprotein
AFU	Alpha-L-fucosidase
ANGs.....	Anghoproteins
ALP.....	Alkaline phosphatase
ALT	Alanine transaminase
Bax.....	Bcl-2 associated
BCLC	System The Barcelona-Clinic- Liver-Cancer system
BCS	Budd-Chiari syndrome
CECT.....	Contrast enhanced helical computed tomography
CEUS.....	Contrast enhanced ultrasound
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-carboxyprothrombin
DNA	Dinucleic acid
EASL.....	European association for the study of the liver
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FDA.....	Food and Drug Administration
FNAB	Fine needle aspiration biopsy
5-FU.....	5-fluorouracil
GCV	Ganciclovir
GGT.....	Gamma-glutamyltranspeptidase
GP73.....	Golgi protein 73
GPC3	Glypican-3
G6P.....	Glucose-6-phosphatase

List of Abbreviations (Cont...)

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
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
ICGR	Indocyanine Green retention rate
ICG R15(%)	Indocyanine Green retention rate at 15 minutes
IGF	Insulin like growth factor
ILP	Interstitial laser photocoagulation
IL-8	Interleukin-8
INR	International normalized ratio
IVC	Inferior vena cava
JISScore	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
MCT	Microwave Coagulation Therapy
MDCT	Multidetector helical CT
MELD	The Model for End Stage Liver Disease
MOVC	Membranous obstruction of the inferior vena cava
MPCT	Multiphasic helical CT
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
PAT	Parenteral anti-schistosomal treatment
PBMCs	Peripheral blood mononuclear cells

List of Abbreviations (Cont...)

PCT.....	Porphyria cutaneatarda
PDGFR.....	Platelet derived growth factor receptor
PEI	Percutaneous ethanol injection
PEIT.....	Percutaneous ethanol injection treatment
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
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
WHO	World Health Organization

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Protocol

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Introduction

Hepatocellularcarcinoma is a major health problem worldwide, with more than 500000 cases diagnosed annually ***(Parkin et al., 2001)***. HCC is the fifth most frequent tumor in the world ***(Anthony, 2001),*** and the most common cause of cancer related death ***(Parkin et al., 2001).*** While the incidence of Hepatocellular carcinoma has reportedly risen over the last5 to 8 years, the survival of those affected has not changed significantly in the last two decades ***(Bosch et al., 2004)***. This is related to both its late detection and the lake of effective therapies for advanced stage disease ***(Bruix & Lovet, 2002).***

Rising Prevalence in Egypt within the last two decades, this is related to both, it is late detection and lack of effective therapies for advanced stage disease. Several factors attribute the high prevalence of Hepatocellular carcinoma including cirrhosis, hepatitis C virus and hepatitis B virus. Up to 80% of Hepatocellular carcinoma develop against a background of cirrhosis of the liver and while it is believed that surveillance of the at risk cirrhotic population could aid earlier detection of the disease and decrease the cancer related mortality rate, our present success is limited by lack of sensitive biomarker ***(Bruix & Lliovet, 2002).***

Currently standard surveillance includes a combination of 6 monthly abdominal ultrasound scan and serum alpha-fetoprotein measurement, but this strategy does not reliably detect early disease. The diagnostic performance of alpha-

fetoprotein is inadequate ***(Sherman. 2001)*** as it is only elevated in 40-60% of cases, while abdominal ultrasonography is difficult in cirrhotic nodular livers and notoriously user dependant ***(Bruix et al., 2001).***

The oncofetal antigen glypican-3(GPC-3) is a heparan sulfate proteoglycans that is expressed more than 70% of Hepatocellular carcinoma ***(Capuro et al 2005).***

When combind with AFP it has sensitivity of up to 82% for HCC detection on a background of viral hepatitis ***(Capurro et al., 2005).*** Measurement of (GPC3) may be of help in the early detection ofHepatocellular carcinoma ***(Beale et al,2008).***

Glypican-3is a member of the glypican family of heparin sulfate proteoglycans, which are linked to the cell surface through a glycosylphosphatidylinositol anchor ***(Filmus,2001).*** GPC3 has been reported to be expressed in the majority (more than 70%) of Hepatocellular carcinoma as a diagnostic marker ***(Jia et al., 2007).***

Aim of the Work

The aim of the present study is:

To evaluate the diagnostic value of glypican-3 (GPC3) in serum for primary hepatocellularcarcinoma (HCC).