A Comparative Study of the Diagnostic and Prognostic Value of Golgi Protein 73 and Alfa-feto Protein in Hepatocellular Carcinoma Before and After Therapeutic Intervention

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بسم الله الرحمن الرحيم

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

صدق الله العظيم
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List of Abbreviations

Abb.	Full term
5`-NPD	5`-Nucleotide phosphodiesterase
8-OHdG	8-hydroxydeoxyguanosine
AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive alpha-fetoprotein
AFU	Alpha L-Fucosidase
AJCC	American Joint Committee on Cancer
ALB	Albumin
ALK.P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
BCLC	Barcelona-Clinic Liver Cancer
BUN	Blood urea nitrogen
CA125	Cancer antigen 125
CA19.9	Cancer antigen 19.9
Cd 68	Cluster of differentiation
CEA	Carcino embryonic antigen
CEA	Carcinoembryonic Antigen
Ck7	cytokeratin 7
CLIP	Cancer of the Liver Italian Program score
CLT	Cadaveric liver transplant
CREAT	Creatinine
CREB	Cyclic adenosine monophosphate
CT	Computed tomography
D bil	Direct bilirubin

List of Abbreviations cont...

Abb.	Full term
DCP	Des-gamma-carboxyprothrombin
dNA	Deoxy Ribonucleic acid
EASL	European Association for the Study of the Liver
ELISA	Enzyme-linked immunosorbent assay
EpCAM	Epithelial cell adhesion molecule
EPO	Erythropoietin
ERK	Extracellular-signal-regulated kinase
GGT	Gamma-glutamyl transferase
GOLM1	Golgi Membrane Protein 1
GOLPH2	Golgi phosphoprotein 2
GP73	Golgi protein 73
GP73tr	Golgi protein 73 terminus
GPC3	Glypican-3
HB	Haemoglobin
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Anti-hepatitis D virus
Hfl	Hepatic focal lesion
HNE	4-hydroxynonenal
HS-AFP	Hepatoma-specific Alfa feto protien
HSP	Heat shock protein
hTERT	Human telomerase reverse transcriptase
ICG	Indocyanine green
IGF-II	Insulin-like growth factor-II

List of Abbreviations cont...

Abb.	Full term
IL 8	Interleukin-8
INR	International normalized ratio
IOUS	Intraoperative ultrasonography
K	Potassium
LDLT	Living donor liver transplant
MAGE-1	Melanoma antigen gene
MELD	Model for end stage liver disease
MHFL	Multiple hepatic focal lesions
Mmp	Matrix metalloproteinase
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mRNA	Messenger ribonucleic acid
MWA	Microwave ablation
Na	Sodium
NAFLD	Nonalcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NPV	Negative predictive value
OS	Overall survival
PAI	Percutaneous Acetic Acid Injection
PDGFR-beta	Platelet-derived growth factor receptor beta
PEI	Percutaneous Ethanal injection
PET	Positron emission tomography
PPV	Pvpositive predictive value
PSA	Prostate specific antigen
PST	Performance status
PTT	Partial thromboplastin time
PVE	Portal vein embolization
RAF	Rapidly Accelerated ibrosarcoma

List of Abbreviations cont...

Abb.	Full term
REBP	Response element binding protein
RFA	Radio frequency ablation
RNA	Ribonucleic acid
ROC	Curvereceiver operating characteristic curve
SCCA	Serum squamous cell carcinoma antigen
Sens	Senstivity
SHARP	Sorafenib HCC Assessment Randomised Protocol
SPDI	Secreted protein discovery initiative
Spec	Specificty
SU	Sunitinib malate
T Bil	Total bilirubin
T.prot	Total proteins
TACE	Trans arterial chemo embolization
TACE-DEB	Trans arterial chemo embolization with drug eluting beads
TGF-β1	Transforming growth factor-beta 1
TKs	Tyrosine kinases
TLC	Total leucocytic count
TMD	Transmembrane domain
TNM	Tumor, lymphnodes and metastasis
UICC	Union Internationale Contre le Cancer
US	Ultrasound
VEGF	Vascular endothelial growth factor

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the second leading cause of cancer-related deaths worldwide. Globally, there are approximately 750000 new cases and 700000 deaths of HCC reported per annum.

Aim of the Study: To evaluate the diagnostic value of serum level of golgi protein 73 (GP73) as a tumor marker for HCC and its prognostic value after trans arterial chemo embolization (TACE) or radiofrequency ablation (RFA), in comparison to alpha-feto protein (AFP).

Patients and Methods: This study will be performed on *60 subjects* from the outpatient Hepatology clinic and inpatient Gastroenterology and Hepatology Department at Ain Shams University Hospital. They will be classified into three groups: *Group I:* Fourty (40) patients with hepatocellular carcinoma who will undergo either RFA or TACE, *Group II:* Ten (10) patients with liver cirrhosis without hepatocellular carcinoma, *Group III:* The control group composed of Ten (10) age and sex matched healthy subjects.

Results: In our study, there was a significant positive correlation between GP73 and AFP values with tumor number and size with p values of 0.001, GP73 levels decreased significantly in patients with HCC after intervention either by RFA or TACE with a p value 0.001

Conclusion: Plasma GP73 is a sensitive and specific serum marker for the diagnosis of HCC and we recommend combination of AFP and GP73 in screening and diagnosis of HCC. Also the marked significant reduction of serum GP73 levels in HCC patients subjected to either RF ablation and TACE proved that GP73 may play a prognostic marker in HCC management.

Keywords: Golgi Protein 73, Alfa-feto Protein, Hepatocellular Carcinoma, Therapeutic Intervention

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the second leading cause of cancer-related deaths worldwide. Globally, there are approximately 750000 new cases and 700000 deaths of HCC reported per annum *(Maluccio and Covey, 2012)*.

Two well-known risk factors for HCC are chronic viral hepatitis B (HBV) and C (HCV), which account for 80%-90% of all HCC cases worldwide. Other risks for HCC include obesity, diabetes, vitamin D deficiency, aflatoxin B1 exposure, alcoholic and non-alcoholic liver cirrhosis *(Xu et al., 2015)*. However, the underlying mechanism of HCC has not been entirely elucidated. Surgical resection and orthotopic liver transplantation are the best curative tools for the long-term survival of HCC patients. However, surgical resection is not feasible in more than 80% of HCC patients because of tumor location, tumor size or severity of the underlying liver disease. Only 5%-15% of HCC patients are potentially resectable *(Zhang et al., 2014)*.

The overall five-year survival rate in patients with HCC is very low, ranging from 5% to 9%. The cumulative five-year recurrence rate is approximately 70% to 80% even after curative surgical resection. Recurrence after resection generally results in a high rate of mortality *(Kumamoto et al., 2013)*.

Current methods for HCC diagnosis are classified into the following main categories: imaging [abdominal ultrasonography, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI)] and laboratory biomarker analysis [serum alpha-fetoprotein (AFP) levels *(Yin et al., 2015)*, However, the diagnostic performance of imaging technologies is unsatisfactory, particularly for the diagnosis of small lesions and early-stage HCC *(Tan et al., 2014)*.

AFP is the most commonly used tumor marker for HCC diagnosis and prognosis prediction, but the false negative rate using AFP level alone is as high as 40% for patients with early-stage HCC. AFP levels remain normal in 15%-30% of all the patients, even patients with advanced HCC *(Zhang et al., 2014)*.

Studies have identified Golgi protein 73 (GP73; also named Golgi phosphoprotein 2(GOLPH2)), as a potential novel HCC serum marker. GP73 is a 400 amino acid, 73 kDa trans membrane glycoprotein that normally resides within the cis-Golgi complex *(Marrero et al., 2005)*.

Subsequent studies showed that the GP73 serum level is elevated in diverse viral and non-viral liver diseases, including hepatitis, cirrhosis and HCC, and also in non-liver malignances *(Tan et al., 2009)*.