



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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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List of Abbreviations

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

List of Abbreviations cont...

Abb.	Full term
<i>D</i> CP.....	<i>Des-gamma-carboxyprothrombin</i>
<i>d</i> NA	<i>Deoxy Ribonucleic acid</i>
<i>E</i> ASL	<i>European Association for the Study of the Liver</i>
<i>E</i> LISA.....	<i>Enzyme-linked immunosorbent assay</i>
<i>E</i> pCAM.....	<i>Epithelial cell adhesion molecule</i>
<i>E</i> PO.....	<i>Erythropoietin</i>
<i>E</i> RK	<i>Extracellular-signal-regulated kinase</i>
<i>G</i> GT.....	<i>Gamma-glutamyl transferase</i>
<i>G</i> OLM1.....	<i>Golgi Membrane Protein 1</i>
<i>G</i> OLPH2.....	<i>Golgi phosphoprotein 2</i>
<i>G</i> P73	<i>Golgi protein 73</i>
<i>G</i> P73tr.....	<i>Golgi protein 73 terminus</i>
<i>G</i> PC3	<i>Glypican-3</i>
<i>H</i> B.....	<i>Haemoglobin</i>
<i>H</i> BeAg.....	<i>Hepatitis B e antigen</i>
<i>H</i> BsAg	<i>Hepatitis B virus surface antigen</i>
<i>H</i> BV.....	<i>Hepatitis B virus</i>
<i>H</i> CC.....	<i>Hepatocellular carcinoma</i>
<i>H</i> CV.....	<i>Hepatitis C virus</i>
<i>H</i> DV.....	<i>Anti-hepatitis D virus</i>
<i>H</i> fl.....	<i>Hepatic focal lesion</i>
<i>H</i> NE.....	<i>4-hydroxynonenal</i>
<i>H</i> S-AFP.....	<i>Hepatoma-specific Alfa fetoprotein</i>
<i>H</i> SP.....	<i>Heat shock protein</i>
<i>h</i> TERT.....	<i>Human telomerase reverse transcriptase</i>
<i>I</i> CG.....	<i>Indocyanine green</i>
<i>I</i> GF-II.....	<i>Insulin-like growth factor-II</i>

List of Abbreviations cont...

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

List of Abbreviations cont...

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

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*).