Hepatoma-Specific AFP (H-S AFP) in the Diagnosis of Hepatocellular Carcinoma

Thesis

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قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and it is one of the major causes of death. HCC is now a rather common malignancy in Egypt which usually develops on top of liver cirrhosis secondary to viral infection. HCC diagnosis is a multistage process including clinical, laboratory, imaging and pathological examinations. The AFP diagnostic accuracy is unsatisfactory and questionable because of low sensitivity, therefore there is a strong demand by clinicians for new HCC-specific biomarkers. The lens culinaris agglutinin (LCA)-reactive alpha-fetoprotein (AFPL3) is percentage of total AFP concentration and it is the major glycoform in the serum of HCC patients

Aim: The aim of this study was to investigate the potential role of Hepatoma-Specific AFP (AFPL3) as a diagnostic non-invasive marker for HCC, in order to add a beneficial diagnostic value in patients with low levels of alpha-fetoprotein (AFP) and suspected to have HCC.

Methods: This study was conducted on **27** HCC patients with and **30** cirrhotic patients with no evidence of HCC; as well as **31** healthy subjects who served as control group.

We determined the level of AFP and AFPL3 for all cases together with full clinical assessment, liver biochemical profile, conventional ultrasound (US), abdominal triphasic CT scan.

Results: We found that there was positive correlation between AFPL3 and total AFP, also AFPL3 was significantly elevated in the HCC group comparing to cirrhosis and control groups. The higher total AFP the higher AFPL3 percentage. The diagnostic sensitivity of AFP at a cutoff 22.6 ng/ml was 83% and the specificity was 83%. The cutoff level of AFPL3 for diagnosis of HCC in this study was 5%, with a sensitivity and

specificity of 96% and 83% respectively. There was a significant elevation of AFPL3 with patient whose total AFP level (10-200) with increasing specificity and PPV to100% at cut off 3.8%. There was no positive correlation between AFPL3 and the number or the size of hepatic focal lesions in HCC patients.

Conclusion:

- AFP-L3 is a useful adjunct marker in the diagnosis of HCC
- In the grey zone patients where AFP determination is alone clueless in the diagnosis of HCC , the addition of AFP-L3 has a 100 % specificity and 100% PPV
- Outside the grey zone patients AFP may suffice in the diagnosis of HCC, where AFP-L3 is not detectable if total AFP is less than10 ng/dl and if total AFP is more than 200 it would obviously trigger calling for another confirmatory modality.
- AFP-L3 offers no correlation to the clinical or ultrasonographic features of tumors

Key words:

- Hepatocellular carcinoma (HCC).
- Alpha-fetoprotein (AFP).
- Hepatoma-Specific AFP (AFPL3).

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List of Abbreviations

AASLD	American Association for the Study of Liver Disease
AFB1	Aflatoxin B1
AFP	Alpha fetoprotein
AFP mRNA	Alpha fetoprotein mRNA
AFPL3	Alpha fetoprotein L3
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AST	Aspartate transaminase
BCCLC	Barcelona Clinic Liver Cancer
CCDS	Color code Duplex sonograph
CEA	Carcinoembryonic antigen
CLDs	Chronic liver disease
CLIP	Cancer of the Liver Italian Program
CT	Computerized tomography
CTA	Computerized tomography arterigraphy
CTAP	Computerized tomography arterioportography
DCP	Des-γ-carboxy prothrombin
ETs	Endothelins
FNA	Fine needle aspiration

GGT	Gamma glutamyl transpeptidase
GGT mRNA	Gamma glutamyl transferase mRNA
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
H-S AFP	Hepatoma –Specific AFP
IARc	International Agency for research on cancer
IGF-II	Insulin-like growth factor β
IL8	Interleukin-8
IOUS	Intraoprative ultrasound
LC	Liver cirrhosis
LCA	Lens-culinaris agglutinins
LCSGJ	Liver cancer study group of Japan
MAGE	Melanoma antigen gen
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
P53	Protein 53
PCR	Polymerase chain reaction
PCT	Porphyria cutanea tarda

PET	Positron emission tomography
PIVKA	Prothrombin induced by vitamin K absence II
PPV	Positive predictive value
RTPCR	Reverse transcription PCR
TGF-B1	Transforming growth factor beta1
TNM	Tumor- nodes-metastasis
TSH	Thyroid stimulating hormone
VIP	Vasoactive intestinal peptide

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most commen cancer in the world with a 5 year survival rate of less than 5% and an incidence of at least one million new patients per year ***(Bruix et al., 2004)***.

It is the most common primary malignant tumor of the liver (approximately 85-90%) ***(El Serag & Rudolph, 2007).***

HCC incidence rate has been increasing over the last two decades of 20th century. In the United States, the reported incidence has increased to 4.7/100,000.The male population, both black and white, is primarily affected. However, the incidence of HCC in eastern Asia and middle Africa is more than five times that of North America. Furthermore, from 1981 to1985 the peak incidence of HCC occurred in patients 80 to 84 years of age, whereas from 1991 to 1995 the peak was noted in persons 74 to79 years of age. The shift in incidence toward younger persons seen over the last two decades coincides with the prevalence of hepatitis C virus infection ***(Jorge and Marrero, 2003).***

Incidence of HCC in Egypt is currently increasing, which maybe the result of a shift in the relative importance of HBV and HCV as primary risk factors. HCC is the second most frequent cause of cancer incidence and mortality among men in

Egypt .Hospital based studies have reported an increase in Egypt (>95%asHCC), from 4.0% in 1993 to 7.3%in 2003 ***(El-Zayaadi et al., 2005).***

Nowadays HCC diagnosis is a multistage process including clinical, laboratory, imaging and pathological examinations. The prognosis of HCC is mostly poor, because of detection at an advanced, non-resectable stage. Potentially curative treatment (surgery) is limited and really possible only for cases with small HCC malignancies. For this reason, more effective surveillance strategies should be used to screen for early occurrence of HCC targeted to the population at risk. So far, the generally accepted serological marker is α-fetoprotein (AFP). Its diagnostic accuracy is unsatisfactory and questionable because of low sensitivity, therefore there is a strong demand by clinicians for new HCC-specific biomarkers (***Stefaniuk et al., 2010).***

Alpha fetoprotein (AFP) is a fetal specific glycoprotein produced primarily by the fetal liver. Normally, its serum concentration falls rapidly after birth and its synthesis in adult life is repressed. However, greater than 70% of HCC patients have a high serum concentration of AFP because of the tumor excretion. Forty years after its discovery, serum AFP remains a most useful tumor marker in screening HCC patients. The normal range for serum AFP levels is 10-20 ng/mL and a level