Circulating mRNA of Lamin B1 for Detection of Early Stages of Hepatocellular Carcinoma

Thesis

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة آية
(٣٢)

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Amani Mohamed

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List of Abbreviations

2DE .....Two dimensional electrophoresis

3D.....Three dimension

ADLD .....Adult-Onset Autosomal Dominant Leukodystrophy

AFP.....Alpha fetoprotein

AFU .....Alpha-L-fucosidase

ALT.....Alanine amino transferase

AST.....Aspartate aminotransferase

AUC .....Area under curve

BCG .....Bromocresol green

BCLC .....Barcelona-Clinic Liver Cancer staging system

CA125 .....Carbohydrate antigen 125

CBC .....Complete blood count

cDNA .....Complementary DNA

CEA .....Carcinoembryonic antigen

CLD .....Chronic liver disease

CT.....Computerized tomography

C_t.....Cycle threshold

DCP .....Des-gamma-carboxyprothrombin

DNA .....Deoxynucleic acid

dNTP.....Deoxyribose nucleotide triphosphate

EASL.....European association for the study of the liver

EDTA.....Ethylene diamine tetraacetic acid

ELISA .....Enzyme linked immunosorbent assay

FN.....False negative

FP.....False positive

List of Abbreviations

GAPDH .....Glyceraldehyde-3-phosphate dehydrogenase

GDNA.....Genomic DNA

GGT m RNA.....Gamma glutamyl transferase

HBsAg.....Hepatitis B surface antigen

HBV .....Hepatitis B virus

HCC.....Hepatocellular carcinoma

HCV.....Hepatitis C virus

HGF.....Hepatocyte growth factor

HP1 .....heterochromatin protein 1

HRP.....Horse radish peroxidase

hTERT mRNA..... Human telomerase reverse transcriptase mRNA

IF.....Intermediate filament

Ig.....Immunoglobulin

IGFII mRNA..... Insulin- like growth factor II-mRNA

INM.....Inner nuclear membrane

INR.....International normalized ratio

IQR.....Interquartile range

LBR .....Lamin B receptor

LDH.....Lactate dehydrogenase

MALDI-TOF .....Matrix-assisted laser desorption / ionization Time of flight mass spectrometry

MAPK .....Mitogen activated protein kinase

MDH .....Malate dehydrogenase

MRI .....Magnetic resonance imaging

mRNA.....Messenger ribonucleic acid

List of Abbreviations

MS .....Mass spectrometry

NAD .....Nicotinamide adenine dinucleotide

NE.....Nuclear envelope

NPC .....Nuclear pore complexes

NPV .....Negative predictive value

OCT1 .....Octamer 1transcription factor

ONM .....Outer nuclear membrane

OS.....Oxidative stress

P5P.....Pyridoxil 5 phosphate

PKCa .....Protein kinase C alpha

PPV.....Positive predictive value

PST.....Performance status test

PT.....Prothrombin time

ROC.....Receiver operating characteristic curve

RT-PCR.....Reverse transcription polymerase chain reaction

SCCA..... Squamous cell carcinoma antigen

SDS.....Sodium deodecyl sulphate

TGFB1 .....Transforming growth factor-β1

TN.....True negative

TNM.....Primary tumor, lymphnode, metastasis staging system

TP.....True positive

US.....Ultrasonography

VEGF .....Vascular endothelial growth factor

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of death worldwide, causing 600,000 deaths annually ***(Terry and Copur, 2013).*** In Egypt, HCC accounts for 4.7% of all liver diseases. Hospital-based studies have reported an overall increase in the relative frequency of all liver cancers in Egypt from approximately 4% in 1993 to 7.3% in 2003, more than 95% of which being HCC ***(El-Garem et al., 2013).***

In an attempt to study the trend of HCC in Egypt and the possible associating risk factors, ***El-Zayadi et al.(2005***) found that 86.9% and 28.4% of the studied HCC cases were positive for hepatitis C virus (HCV) antibodies and hepatitis B surface antigen (HBsAg) respectively. Indeed, liver cirrhosis is the major risk factor for HCC worldwide and is mainly due to chronic HCV or HBV infection and alcohol intake ***(Gomaa et al., 2009).***

Patients diagnosed at an early stage of HCC have the best prognosis, where resection and transplantation achieve the best outcomes in well-selected candidates, with a 5-year-survival rate of 50 to 70% ***(Llovet et al., 2004).*** Unfortunately, only 10-20% of primary HCCs are

resectable at the time of diagnosis, therefore, surveillance, currently based on abdominal ultrasound (US) and serum alphafetoprotein (AFP), is recommended for all cirrhotic patients and other specific risk groups every 6 months. AFP is currently considered 'the golden standard' of serum markers for HCC. However, the usefulness of AFP testing for the population at risk is seriously questioned. It has shown poor diagnostic values for early HCC. Applying a cut-off value > 100 μg/L, its sensitivity ranges from 20%-30% for potentially resectable tumors of less than 3 cm in diameter. Moreover, the AFP cut-off level for the diagnosis of HCC is still a subject of debate. Assay of lens culinaris-reactive AFP, which is also known as AFP-L3, it is the main glycoform of AFP in the serum of HCC patients increased the sensitivity of AFP to >50% at the cut-off level of 15% of total AFP**,** yet it is not routinely measured ***(Gomaa et al., 2009 and Sun et al., 2010).***

Currently, US represents the primary radiologic tool for HCC surveillance of at-risk populations. However, US has limited sensitivity (<60%) to detect small HCC especially in obese patients and those with underlying cirrhosis. The gold standard test for diagnosis of HCC is spiral computerized tomography (C.T.) which has advanced sensitivity and specificity over US. Unfortunately, its use in HCC surveillances have been limited, since the diagnostic