Evaluation of Transient Elastography in Prediction of De novo Recurrence of Hepatocellular Carcinoma after Radiofrequency Ablation

Thesis

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By

Sayed Ahmed Sayed

Master degree of Tropical medicine
Faculty of Medicine-Ain Shams University

Under Supervision of

Prof. Nadia Abdelaty Abdelkader

Professor of Tropical Medicine
Faculty of Medicine-Ain Shams University

Prof. Mostafa Hamed Abdelaleem

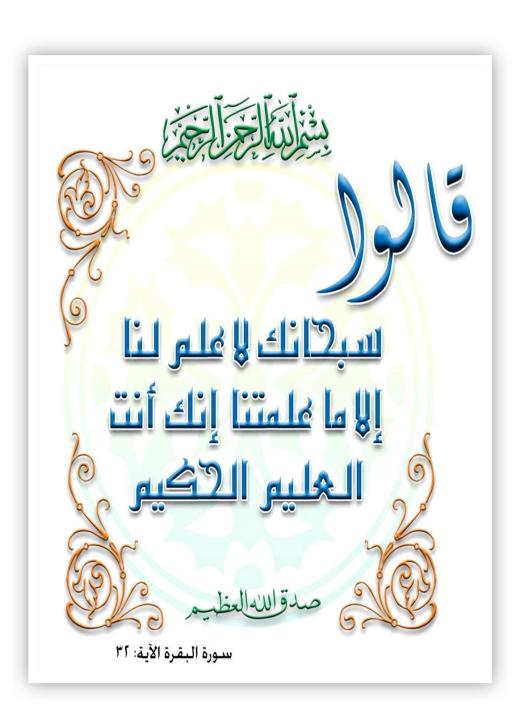*Professor of Tropical Medicine*
Faculty of Medicine-Ain Shams University

Dr. Heba Ismail Saad

Lecturer of Tropical Medicine
Faculty of Medicine-Ain Shams University

Prof. Mohamed El-Gharib Abo El-maaty

Professor of Radiodiagnosis
Faculty of Medicine-Ain Shams University

Faculty of Medicine
Ain Shams University
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قَالُوا

سبحانك لا علم لنا

إلا ما علمتنا إنك أنت

العليم الحكيم

صدق الله العظيم

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List of Abbreviations

Abbr.	Full-term

A1ATD .... Alpha-1-Antitrypsin Deficiency
AAR .... AST – ALT ratio
AASLD .... American Association of Liver Disease
AFB1 .... Aflatoxin B1
AFP .... Alpha Feto Protein
AFTs .... Aflatoxin
AIH .... Autoimmune Hepatitis
AJCC .... American Joint Committee on Cancer
ALD .... Alcoholic Liver Disease
ALT .... Alanine Transaminase
API .... Age-Platelet index
APASL .... Asian Pacific Association for the Study of the Liver
APRI .... Age Platelet Ratio Index
ARFI .... Acoustic radiation force impulse elastography
AST .... Aspartate aminotransferase
AUV .... Area under the curve
BCLC .... Barcelona-Clínic Liver Cancer Staging System
BCS .... Budd-Chiari syndrome
BMI .... Body Mass Index
BUN .... Blood Urea Nitrogen
CAP .... Controlled Attenuation Parameter
CDS .... Cirrhosis Discrinination Score
CEUS .... Contrast-Enhanced Ultrasound
CHB .... Chronic Hepatitis B
CHC .... Chronic hepatitis C
CK19 .... Cytokeratin 19
CLD .... Chronic Liver Disease
CLIP .... Cancer of the Liver Italian Program Score

CSCs ....*Cancer Steam Cells*
CT ....*Computed tomography*
CTP ....*Child-Turcotte-Pugh*
CUPI ....*Chinese University Prognostic Index*
DAAs ....*Direct Antiviral Agents*
DCP ....*Des-Gamma-Carboxy Prothrombin*
DEB-*TACE*..........*TACE Performed with Drug-Eluting Beads*
DHS ....*Demographic Health Survey*
DNA ....*Double strand Nucleic Acid*
DWI.....................*Diffusion-Weighted Imaging*
ECM....................*Mxtracellular Matrix*
ECOG...................*Eastern Cooperative Oncology Group Performance Status*
EGF ....*Epidermal growth factor*
EGFR..................*Epidermal growth factor receptor*
FDA ....*Food and Drug Administration*
FGFR..................*fibroblast growth factor receptor*
FIB4....................*Fibrosis 4*
FUO ....*Fever Of Unknown Origin*
GETCHC ....*Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire*
GGT ....*Gamma-glutamyl transferase*
GPC3...................*Glypican-3*
HA....................... *Hyaluronic acid*
HAP ....*Hepatoma Arterial Embolization Prognostic Score*
HBV....................*Hepatitis B Virus*
HCC ....*Hepatocellular carcinoma*
HCV....................*Hepatitis C Virus*
HDV.................... *Hepatitis D Virus*
HFL ....*Hepatic Focal Lesion*
HGF....................*Hepatocyte growth factor*
HGRF .... *Hepatoma-derived growth factor*
HH ....*Hereditary Hemochromatosis*
HIFU ....*High-Intensity Focused Ultrasound*

HSP70.................*Heat Shock Protein 70*
HV......................*Hepatic Vein*
HZ......................*hertz*
HNBG................*Hepatic Venous Pressure Gradient*
IDR ....*Intra Hepatic Distant Recurrence*
IGF-*2* ....*Insulin like Growth Factor-2*
IGFR..................*Insulin-like Growth Factor Receptor*
IL-*6* ....*Interleukin 6*
IL-*8* ....*Interleukin 8*
INFs...................*Interferons*
INR ....*International normalized ratio*
IQR ....*Inter interquartile ange*
IVC......................*Inferior Vena Cava*
K..........................*Potassium*
KPa ....*kilopascals*
LDLT ....*living-Donor Liver Transplantation*
LOH ....*Loss of heterozygosity*
LR ....*Liver Resection*
LS........................*Liver Stiffness*
LSM ....*Liver Stiffness Measurment*
LT........................*Liver Transplant*
LYVE1.................*Lymphatic vessel endothelial hyaluronan receptor 1*
M.........................*Metastasis*
MAA....................*macroaggregates of albumin*
MABK.................*mitogen-activated protein kinases*
MBT....................*13C-Methacetin Breath Test*
MDCT.................*Multidetector CT*
MELD ....*Model for End-Stage Liver Disease*
MFAP-*4* ....*Micro Fibril-Associated Glycoprotein 4:*
MRE....................*Magnetic resonance elastography*
mRECIST............*Modified Response Evaluation Criteria in Solid Tumors*
MRI.....................*Magnetic resonance imaging*

mRNA ....*Messenger ribonucleic acid*
mTOR................*Mammalian target of rapamycin*
MWA...................*Microwave Ablation*
N ....*Nodal*
Na........................*Sodium*
NAFLD ....*Nonalcoholic Fatty Liver Disease*
NASH.................*Nonalcoholic Steatohepatitis*
NICTH ....*Non-Islet Cell Tumor Hypoglycemia*
NIMs ....*Noninvasive Markers*
NPV....................*Negative Predictive Value*
OR......................*Odds Ratio*
OS ....*Overall Survival*
OV ....*Oesophageal Varices*
PBC....................*Primary Biliary Cirrhosis*
PDFGRα.............*platelet-derived growth factor receptor α (PDFGRα)*
PEI.....................*Percutaneous Ethanol Injection*
PET.....................*Positron Emission Tomography*
PHT....................*Portal Hypertension*
PLT ....*Platelate*
PI3k....................*Phosphoinositide-3 kinase*
PICP ....*Procollagen type I carboxy terminal peptide*
PIVKA-II ....*Protein induced by vitamin K absence or antagonist II*
PNS ....*Paraneoplastic Syndrome*
PNS....................*Paraneoplastic Syndrome*
PS........................*Performance status*
PSR.................... *Platelet-to-Spleen Ratio*
PT.......................*Prothrombin Time*
PTEN .... *Phosphatase and tensin homolog*
PTH ....*Parathyroid Hormone*
PTHrP ....*Parathyroid Hormone Related Peptide*
PTT.....................*Partial Thrombopastin Tme*
qRT-PCR.............*Quantitative Reverse Transcription PCR*

RAF..................... *Rapidly Accelerated Fibrosarcoma*
RCT..................... *Randomized Control Trial*
RET..................... *rearranged during transfection*
RFA..................... *Radiofrequency Ablation*
RFS..................... *Recurrence Free Survival*
RNA.................... *Ribonucleic Acid*
Roc..................... *receiver operating characteristic*
ROS..................... *Reactive Oxygen Species*
RR...................... *Relative Risk*
SBRT................... *Stereotactic Body Radiation Therapy*
SCCA.................. *Squamous Cell Carcinoma Antigen*
SCD..................... *Skin Capsule Distance (*
SPIO................... *Superparamagnetic Iron Oxide*
SR....................... *success rate*
SSI...................... *Supersonic Shear Imaging*
SVR..................... *Sustained Virological Response*
SWE.................... *Shear wave elastography*
T......................... *Tumor*
TACE.................. *Trans Arterial Chemoembolization*
TARE.................. *Trans Arterial Radioembolization*
TE....................... *Transient elastography*
TGF-*β*1.............. *Transforming growth factor b1*
UCSF.................. *University of California, San Francisco*
UICC................... *International Union against Cancer*
US...................... *Ultrasound*
USA.................... *United states of America*
VEGF................. *Vascular Endothelial Growth Factor*
VM..................... *Valid Measurements*
WBC................... *White Blood Cell*

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and it is a common cause of death in patients with chronic liver disease *(Forner, et al., 2012)*.

The curative treatment options for HCC that are currently available are surgical resection, liver transplantation and radio-frequency ablation (RFA) *(Bruix and Sherman, 2011).*

Among these options, RFA has been accepted as an effective nonsurgical curative treatment modality for early-stage HCC tumors (solitary tumors, 5 cm in diameter or fewer than 3 nodules, 3 cm in Diameter *(Livraghi et al., 2008)*.

Radiofrequency ablation achieves a satisfactory local response rate, with more than 80% complete ablation in most studies *(Lencioni, 2010).* Several recent randomized controlled trials and repeated meta-analyses have shown that the rates of overall survival (OS) and recurrence-free survival after RFA are comparable with those after surgical therapy *(Cho et al., 2011)*.

Despite progressive improvements in the efficacy of RFA, the survival of patients with HCC who undergo RFA remains disappointing, mainly due to frequent intrahepatic recurrence of HCC after RFA *(Lencioni, 2010).*

There are two types of intrahepatic recurrence of HCC after RFA: local tumor progression and de novo recurrence. Local tumor progression, known as local recurrence results from direct dissemination of the original tumor along the peripheral margin of the ablated lesion, while de novo recurrence accounts for multicenter occurrence of a HCC tumor in a location remote from the ablated lesion *(Goldberg et al., 2009)*.

Local factors which include tumor location, tumor numbers, direct invasion into vessels, and insufficient safety margins have been identified as significant predictors of local recurrence *(Zytoon et al., 2007)*, whereas the necroinflammatory activity of hepatitis and the degree of liver fibrosis or cirrhosis have been shown to be significantly associated with de novo recurrence *(Imamura et al., 2003).*

Several studies have shown that inflammation-based prognostic scores including a combination of serum CRP and albumin as the Glasgow Prognostic Score (GPS), a combination of neutrophil and lymphocyte counts as the neutrophil to lymphocyte ratio (NLR), and a combination of albumin and lymphocyte counts as the Prognostic Nutritional index (PNI) are associated with survival in patients with HCC *(Ishizuka et al., 2012).*