# Role of Liver Transplantation in Management of Hepatocellular Carcinoma

Essay

*Submitted for Partial Fulfillment of Master Degree in*
*Internal Medicine*

Presented by

Atef Fahmy Ahmed Sallam
(M.B., B.Ch.)
Mansoura University

Supervised by

**Prof. Dr. Khaled Zakaria El Karmouty**
*Professor of Internal Medicine, Gastroenterology & Hepatology*
*Faculty of Medicine – Ain Shams University*

**Dr. Eslam Safwat Mohamed**
*Lecturer of Internal Medicine, Gastroenterology & Hepatology*
*Faculty of Medicine – Ain Shams University*

**Dr. Ossama Ashraf Ahmed**
*Lecturer of Internal Medicine, Gastroenterology & Hepatology*
*Faculty of Medicine – Ain Shams University*

**Faculty of Medicine**
**Ain Shams University**
**2013**

# LIST OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

| Fig. No | Title | Page |
|---|---|---|

# Chapter 1

## Hcc: An overview

# ACKNOWLEDGEMENT

*First of all, I would like to Thank **Allah** who granted me the strength to accomplish this work.*

*I would like to express my gratefulness and respect to **Prof. Dr. Khaled Zakaria El Karmouty,** Professor of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain Shams University, for his moral and scientific support and for giving me the honor to be his student and to work under his supervision and valuable guidance.*

*Special thanks and deepest gratitude to **Dr. Eslam Safwat Mohamed,** Lecturer of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain Shams University, for his constructive and instructive comments and valuable suggestions.*

*I would like to thank **Dr. Ossama Ashraf Ahmed,** Lecturer of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain Shams University, for his supervision and encouragement throughout the practical part of this work.*

*My deepest gratitude I extend to my whole family who offered me support, advice and motivation.*

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AFB1** | Aflatoxin B1 |
| **AFP** | Alpha-fetoprotein |
| **AFU** | Alpha-L-fucosidase |
| **ALT** | Alanine transaminase |
| **ATT** | Alpha-1 antitrypsin |
| **BCLC** | Barcelona Clinic Liver Cancer |
| **CA 125** | Cancer antigen 125 |
| **CC** | Cholangio carcinoma |
| **CdK4** | Cyclin dependent kinase |
| **CDKs** | Cyclin-dependent kinases |
| **CHF** | Chronic heart failure |
| **CLIP** | Cancer of the Liver Italian Program |
| **CLT** | Cadaveric liver transplantation |
| **CsA** | Cyclosporine |
| **CT** | Computed tomography |
| **CUPI** | Chinase university prognostic index |
| **CYP 450** | cytochrome P 450 |
| **DCP** | Des-Y-carboxyl prothrombin |
| **ELIZA** | Enzyme linked immunosorbant assay |
| **ES** | Endostatin |
| **EUS** | Endoscopic ultrasonography |
| **EUS-FNA** | EUS-Fine Needle Aspiration |
| **FDG** | Fluorodeoxy glucose |
| **FDG** | Flurodeoxyglucose |
| **FNA** | Fine Needle Aspiration |
| **GGT** | Gamma-glutamyl transpeptidase |
| **GGT II** | Gamma-glutamyltransferase isoenzyme II |
| **GPC3** | GIypican-3 |

# LIST OF ABBREVIATIONS (CONT.)

| | |
|---|---|
| **H pylori** | Helicobacter pylori |
| **HBeAg** | Hepatitis B envelop antigen |
| **HBsAg** | Hepatitis B Surface Antigen |
| **HBV** | Hepatitis B virus |
| **HCC** | Hepatocellular carcinoma |
| **HCC/CC** | Combined HCC and cholangiocellular carcinoma |
| **HCCR** | Human cervical cancer oncogene protein |
| **HCV** | Hepatitis C virus |
| **HIF1** | Hypoxia inducible factor 1 |
| **HSP** | Heat shock protein |
| **ICAM1** | Intercellular adhesion molecule-1 |
| **IFN-a** | Interferon a |
| **IGF2R** | Insulin-like growth factor 2 receptor |
| **IGF-II** | Insulin like growth factor II |
| **IL-1** | Interleukin 1 |
| **IL-6** | Interleukin 6 |
| **INR** | Internatioonal normalized ratiow |
| **JIS** | Japanese Integrated System |
| **LCA** | Lens culinaris agglutinin |
| **LCSGJ** | Liver cancer study group of japan |
| **LDLT** | Living donor liver transplantation |
| **LOH** | Loss of heterozygosity |
| **LT** | Liver transplantation |
| **MDCT** | Multiphase dynamic CT |
| **MELD** | Model for end-stage liver disease |
| **MMP** | Matrix metalloproteinases |
| **MRI** | Magnetic resonance imaging |

# LIST OF ABBREVIATIONS (CONT.)

| | |
|---|---|
| **MTOR** | Mammalian target of Rapamycin |
| **MVD** | Microvessel density |
| **NASH** | Non Alcoholic Steatohepatitis |
| **NCLCCAA** | National Committee on Liver Cancer of the Chinese Anti cancer Association |
| **NHL** | Non Hodgkin's lymphoma |
| **NS3** | Non Structural 3 |
| **OLT** | Orthotopic liver transplantation |
| **OPTN** | Organ procurement transplantation network |
| **P53** | Protein 53 |
| **PAI-1** | Plasminogen activator inhibitor-1 |
| **PBC** | Primary billary cirrhosis |
| **PCNA** | Proliferating cell nuclear antigen |
| **PDECGF** | Platelet-derived endothelial cell growth factor |
| **PEI** | Percutaneous ethanol injection |
| **PELD** | Pediatric end-stage liver disease |
| **PET** | Positron emissioh tomography |
| **PIAEI** | Percutaneous Intra-arteriai Ethanol Injection |
| **PIVKA-II** | Prothrombin induced by vitamin K absence or antagonist II |
| **PSC** | Primary sclerosing cholangitis |
| **PST** | Performance status test |
| **PT** | Prothrompine time |
| **RFA** | Radiofrequency ablation |
| **RTA** | Relatives of telomerase activity |
| **SRT** | Stereotactic radiotherapy |
| **SSTR** | Somatostatin receptors |
| **TACE** | Transcatheter arterial chemoembolization |

# LIST OF ABBREVIATIONS (CONT.)

| | |
|---|---|
| **TGF** | Transforming growth factor |
| **TGFB** | Transforming growth factor B |
| **TNF** | Tumor necrosis factor |
| **TNF-a** | Tumor necrosis factor-a |
| **TNM** | Tumor node metastasis |
| **TP** | Thymide phosphorylase |
| **TP53** | Tumor Protein p53 |
| **TSP** | Thrompoplastin |
| **UCLA** | University of California and Los Angeles |
| **UCSF** | University of California and san Francisco |
| **uPA** | Urokinase plasminogen activator |
| **uPAR** | Urokinase plasminogen activator receptor |
| **US** | Ultrasound |
| **VEGF** | Vascular endothelial growth factor |
| **vER** | variant estrogen receptor |
| **w/ER** | Wild-type estrogen receptor |
| **5 FU** | 5-fluorouracil |

# Introduction and Aim of the Work

## Introduction:

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the third most common cause of cancer-related death ***(Sanyal et al., 2010).***

Most of HCC patients are asymptomatic and discoverd only during screening program for cirrhosis or liver transplantation ***(Abdel-Wahab et al., 2000).***

A common presentation of HCC is sudden decompansation in a patient known to have cirrhosis such as ascites, encephalopathy, jaundice, or varicial bleeding ***(Jema, 2011)***

Approximately 748,300 new cases of HCC were diagnosed in 2008, and 695,900 patients died of the disease; these statistics underline the high mortality rate of this type of cancer ***(Ferlay et al., 2008)***

Early diagnosis and appropriate determination of extent of HCC and hepatic function are critical in optimizing treatment planning and improving survival rates advances in imaging techniques have improved the ability to carefully evaluate patients with HCC. Three important goals should be addressed when evaluating patients with HCC which are, confirmation of diagnosis,

assessment of hepatic functional reserve and staging of extent of disease ***(El-Serag et al., 2002).***

The standard surgical management for patients with HCC consists of locoregional ablation, surgical resection, or liver transplantation, depending on the state of the liver. Eighty percent of patients initially presenting with HCC are unresectable**,** either due to the extent of tumor or the level of underlying hepatic dysfunction. While in patients with no evidence of cirrhosis and good hepatic function, resection has been the treatment of choice, it is contraindicated in patients with moderate to severe cirrhosis (Child class B or C), leaving these patients with liver transplantation as the only option ***(Thomas et al., 2010)***.

Moreover, transplantation is the optimal treatment even for small, otherwise resectable HCC. This is a reflection of a number of factors. Liver transplantation is the most beneficial oncologic treatment, which most likely results in a resection with microscopically negative margins .Most HCCs are multifocal, arising from a "field defect" in the liver; though pre-neoplastic lesions may not be visible at time of operation, they are likely to continue to evolve into new primary HCCs. Furthermore, transplantation also eliminates cirrhosis and restores normal hepatic function. However, limited organ availability mandates the restriction of transplantation to only those patients with early stage tumors. Organ Procurement Transplant Network (OPTN) data confirm the evolution of liver transplantation from futile to the first choice therapy for selected patients ***(Pelletier et al., 2009)***.

# Aim of the Work

A trial to disclose the updates in diagnosis, treatment, prognosis and early survillance of hepatocellular carcinoma and to introduce liver transplantation as a treatment modality for this common problem in Egypt .

# Epidemiology of HCC

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the third most common cause of cancer-related death ***(Sanyal et al., 2010).***

It is one of the most common solid tumors in the world and accounts for 500.000 deaths every year Also, HCC is the fifth most common cancer in men and it is the eighth in women worldwide ***(Parkin et al., 2005).***

HCC causes significant public health problems, especially in association with chronic hepatitis B or C. The observation that half of HCC cases and deaths are estimated to occur in China indicates that hepatitis B virus (HBV) infection plays a major carcinogenic role in global HCC epidemiology ***(Ferlay et al., 2008).*** Moreover, the incidence of liver cancer is high not only in developing countries but has also been increasing among most racial and ethnic groups in developed countries, such as the United States, as a result of hepatitis C virus (HCV) infection and nonalcoholic steatohepatitis (NASH) ***(Ahmed et al., 2008).***

HCC accounts for 70% to 85% of all cases of primary liver cancer except in some parts of Philippines and Thailand where intrahepatic cholangiocarcinoma is very common ***(McGlynn et al., 2001).***

Unfortunately in Egypt HCC was the 2nd most frequent cancer for male after bladder and constituted 13% of all cancers for female it was the 4th after breast, NHL, and leukaemia and constituted 4.1% of all cancers ***(El-Attar, 2005).***

HCC proportion has increased from 4% to 7.2% among chronic liver disease patients ***(El-Zayadi et al., 2005).***

## Geographical Variation in Incidence:

Approximately 748,300 new cases of HCC were diagnosed in 2008, and 695,900 patients died of the disease; these statistics underline the high mortality rate of this type of cancer ***(Ferlay et al., 2008).***

The frequency with which HCC occur varies in different region with high incidence are eastern and south eastern Asia and in most of Sub-Saharan Africa intermediate incidence occur in eastern and southern Europe, the Caribbean, central America and Western Asia ***(Kew, 2002).***

The exact explanation of this variation is unknown but in general high incidence rates correlate strongly with the prevalence of HBV infection. For example, in china (very high incidence of HCC), the prevalence rate of HBV surface antigen carriers was between 10% and 20% ***(El-Serag et al., 2001).***

The incidence of HCC largely varies according to the geographic area, although it is usually higher in developing