Recent Trends in Management of Hepatocellular Carcinoma

Thesis
Submitted for fulfillment of M.D in general surgery

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Faculty of Medicine
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*****
# Contents

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim of the work</td>
<td>1</td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td><strong>Review of lecturer</strong></td>
<td></td>
</tr>
<tr>
<td>Surgical anatomy of the liver</td>
<td>3</td>
</tr>
<tr>
<td>Epidemiology of Hepatocellular carcinoma</td>
<td>20</td>
</tr>
<tr>
<td>Risk factor and pathology of Hepatocellular carcinoma</td>
<td>22</td>
</tr>
<tr>
<td><strong>Diagnosis of Hepatocellular carcinoma</strong></td>
<td>41</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>41</td>
</tr>
<tr>
<td>Radiological evaluation</td>
<td>44</td>
</tr>
<tr>
<td>Evaluation of functional hepatic reserve</td>
<td>53</td>
</tr>
<tr>
<td><strong>Treatment of Hepatocellular carcinoma</strong></td>
<td>58</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>60</td>
</tr>
<tr>
<td>Ablative therapy</td>
<td>105</td>
</tr>
<tr>
<td>Image - guided transcatheter tumor therapy</td>
<td>129</td>
</tr>
<tr>
<td>Systemic targeted therapy</td>
<td>144</td>
</tr>
<tr>
<td>Role of stem cell in treatment</td>
<td>146</td>
</tr>
<tr>
<td><strong>Patient and Methods</strong></td>
<td>154</td>
</tr>
<tr>
<td>Results</td>
<td>163</td>
</tr>
<tr>
<td>Discussion</td>
<td>173</td>
</tr>
<tr>
<td>Summary and conclusion</td>
<td>177</td>
</tr>
<tr>
<td>References</td>
<td>179</td>
</tr>
<tr>
<td>Arabic summary</td>
<td></td>
</tr>
</tbody>
</table>
**List of Tables**

1- Liver anatomy classification 11
2- Differences between fibrolamellar carcinoma and traditional HCC 28
3- The American Joint committee on cancer (AJCC) stage grouping 34
4- Child-Pugh's scoring system 36
5- Okuda classification 37
6- Cancer of the Liver Italian Program (CLIP) score 38
7- Treatment Options for Hepatocellular Carcinoma 59
8- The "Milan Criteria" defined by Mazzaferro in 1996 80
9- Prognostic Risk Score Grading for Tumor Recurrence 92
10- Definition of best response according to WHO or RECIST criteria 131
11- Liver stem/progenitor cells 147
12- Patients' demographic characteristics 164
13- Complications for each method. 167
14- Early outcome 169
15- Psychological and physical welfare scores among studied groups 170
16- Overall patients’ survival rates during the following up period. 171
17- Recurrence-free survival rates during the following up period 172
List of Figures

1- Diaphragmatic aspect of the liver 5
2- Porta hepatis and features of the visceral surface of the liver 5
3- Anterior view of the liver 7
4- Hepatic "true" lobar and segmental divisions 8
5- Liver segmental anatomy. The eight segments of the liver as defined by Couinaud 9
6- Exploded diagrammatic sketch of the liver 13
7- The four most common variations of the hepatic arterial system 14
8- The "returning loop" of the left branch at the junction of medial and lateral segments 15
9- Diagram to show the intrahepatic distribution of the hepatic artery 17
10- Diagram of the intrahepatic distribution of the hepatic veins 21
11- Geographic distribution of HCC 22
12- Histological differentiation of hepatocellular carcinoma showing cytological and architectural features 31
13- BCLC staging system 39
14- Spider naevi 42
15- Gynecomastia due to liver cell failure 42
16- Hepatosplenomegally with ascites 43
17-Small nodule measuring less than 2 cm located in the right lobe 45
18- The portal branch to segment 7 (P7) 47
19- Contrast-enhanced CT scan demonstrating multifocal hepatocellular carcinoma 47
20- MRI of hepatocellular carcinoma 48
21- The transverse section [T1 with contrast] and coronal section [T2 without contrast] of MRI images demonstrate hypervascular tumor 50
22- Percutaneous liver biopsy 52
23- Superextended hepatectomies 64
24- Major hepatectomies 65
<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-</td>
<td>Limited hepatectomies</td>
</tr>
<tr>
<td>26-</td>
<td>The “laparoscopic segments”</td>
</tr>
<tr>
<td>27-</td>
<td>Laparoscopic left lateral sectionectomy for HCC</td>
</tr>
<tr>
<td>28-</td>
<td>Laparoscopic atypical resection of segment 8 for HCC</td>
</tr>
<tr>
<td>29-</td>
<td>Laparoscopic segmentectomy 4b for HCC</td>
</tr>
<tr>
<td>30-</td>
<td>Laparoscopic atypical resection of segment 2 as a “bridge” to liver transplantation</td>
</tr>
<tr>
<td>31-</td>
<td>Port placement for resection of lesions located in segments 2–5 and for right hepatectomy</td>
</tr>
<tr>
<td>32-</td>
<td>Port placement for resection of lesions located in segment 6</td>
</tr>
<tr>
<td>33-</td>
<td>Venovenous bypass system in place during the anhepatic phase of transplantation Procedure</td>
</tr>
<tr>
<td>34-</td>
<td>Supra-hepatic vena caval anastomosis during implantation of the donor liver</td>
</tr>
<tr>
<td>35-</td>
<td>Complete hepatic transplantation procedure</td>
</tr>
<tr>
<td>36-</td>
<td>RFA for HCC</td>
</tr>
<tr>
<td>37-</td>
<td>CT scan image of HCC before and after RFA</td>
</tr>
<tr>
<td>38-</td>
<td>The NanoKnife generator</td>
</tr>
<tr>
<td>39-</td>
<td>The NanoKnife probe</td>
</tr>
<tr>
<td>40-</td>
<td>Following NanoKnife IRE treatment, blood vessels, ducts, and other collagenous structures in the treated area remain viable</td>
</tr>
<tr>
<td>41-</td>
<td>Vascular supply of HCC. Angiogram just prior to TACE</td>
</tr>
<tr>
<td>42-</td>
<td>Schematic of the vascular supply of HCC</td>
</tr>
<tr>
<td>43-</td>
<td>Transarterial chemoembolization in a patient with unresectable HCC</td>
</tr>
<tr>
<td>44-</td>
<td>Three-month, sequential MRI (a, b, c, d, e) axial images of the liver after TACE</td>
</tr>
<tr>
<td>45-</td>
<td>Pre- (a) and post-TACE (b), axial, contrastenhanced, MRI images show the tumor (arrows) with mild RECIST response but significant EASL-based response, indicated by significant necrosis</td>
</tr>
<tr>
<td>46-</td>
<td>Loading beads</td>
</tr>
<tr>
<td>47-</td>
<td>Drug distribution</td>
</tr>
</tbody>
</table>
48- Combined intraarterial 5-FU and S.C. IFN-α therapy (FAIT) protocol; one cycle

49- Intra- and extrahepatic sources of stem cells

50- HCC in right lobe of the liver (segment VI)

51- Marking of resection Line with diathermy

52- Radiofrequency device used 1cm away from the margin of the tumor for haemostasis

53- Cutting through the liver parenchyma using scalpel

54- Cutting through the liver parenchyma using scissor

55- The dissected tumor with 1cm safety margin before complete excision

56- Cut surface of the liver after resection

57- Resected specimen

58- Cut surface of resected specimen
**LIST OF GRAPHS**

1- Comparison between resection group and RFA group regarding sex 165
2- Comparison between resection group and RFA group regarding cause of liver cirrhosis 165
3- Comparison between resection group and RFA group regarding tumor size 166
4- Comparison between resection group and RFA group regarding AFP 166
5- Graph showing complications of resection group 168
6- Graph showing complications of RFA group 168
7- Comparison between resection group and RFA group regarding Early outcome 169
8- Comparison between resection group and RFA group regarding Psychological and physical welfare 170
9- Comparison between resection group and RFA group regarding Overall patients’ survival rates 171
10- Comparison between resection group and RFA group regarding overall Recurrence-free survival rates 172
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>BCAA</td>
<td>Branched-chain amino acid</td>
</tr>
<tr>
<td>BCLC</td>
<td>Barcelona Clinic Liver Cancer</td>
</tr>
<tr>
<td>BM</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>CCI4</td>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td>CLIP</td>
<td>The cancer of the liver italian program</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CSCs</td>
<td>Cancer stem cells</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>cTACE</td>
<td>Conventional transarterial chemoembolization</td>
</tr>
<tr>
<td>CP</td>
<td>Child–Pugh</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>DEB</td>
<td>Drug-Eluting Beads</td>
</tr>
<tr>
<td>EASL</td>
<td>European Association for the Study of Liver</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
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<tr>
<td>EPCs</td>
<td>Endothelial precursor cells</td>
</tr>
<tr>
<td>ERCP</td>
<td>Endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>ESCs</td>
<td>Embryonic stem cells</td>
</tr>
<tr>
<td>EST</td>
<td>Endoscopic Sclerotherapy</td>
</tr>
<tr>
<td>EVL</td>
<td>Endoscopic variceal-band ligation</td>
</tr>
<tr>
<td>FAIT</td>
<td>Fluorouracil arterial infusion and IFN therapy</td>
</tr>
<tr>
<td>FLHCC</td>
<td>Fibrolamellar HCC</td>
</tr>
<tr>
<td>GIAS</td>
<td>Gastrointestinal Anastomosis Stapler</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPCs</td>
<td>Human hepatic progenitor cells</td>
</tr>
<tr>
<td>HR</td>
<td>Hepatic Resection</td>
</tr>
<tr>
<td>HSC</td>
<td>Hematopoietic stem cells</td>
</tr>
<tr>
<td>ICG</td>
<td>Indocyanine green</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>IL2</td>
<td>Interlukin2</td>
</tr>
<tr>
<td>IOUS</td>
<td>Intraoperative ultrasonography</td>
</tr>
<tr>
<td>iPS</td>
<td>Induced pluripotent stem cell</td>
</tr>
<tr>
<td>IRE</td>
<td>Irreversible Electroporation</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>LDLT</td>
<td>Living donor liver transplantation</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>MCT</td>
<td>Medium-chain triglyceride</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MSC</td>
<td>Mesenchymal stem cells</td>
</tr>
<tr>
<td>MWA</td>
<td>Microwave Ablation</td>
</tr>
<tr>
<td>N/C</td>
<td>Nuclear/Cytoplasmic</td>
</tr>
<tr>
<td>NASH</td>
<td>Nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>OCPs</td>
<td>Oral contraceptive pills</td>
</tr>
<tr>
<td>OLT</td>
<td>Orthotopic liver transplantation</td>
</tr>
<tr>
<td>PEI</td>
<td>percutaneous ethanol injection</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
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<tr>
<td>PVA</td>
<td>Polyvinyl Alcohol</td>
</tr>
<tr>
<td>PVE</td>
<td>Portal vein embolization</td>
</tr>
<tr>
<td>PVT</td>
<td>Portal venous thrombus</td>
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<tr>
<td>PVTT</td>
<td>portal venous tumor thrombus</td>
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<tr>
<td>RCTs</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td>RECICL</td>
<td>Response evaluation criteria in cancer of the liver</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
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<tr>
<td>RFA</td>
<td>Radio frequency ablation</td>
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<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
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<tr>
<td>SMA</td>
<td>Superior mesenteric artery</td>
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<tr>
<td>TACE</td>
<td>Transcatheter arterial chemoembolization</td>
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<tr>
<td>TACI</td>
<td>Transarterial Chemoinfusion</td>
</tr>
<tr>
<td>TAE</td>
<td>Transarterial embolization</td>
</tr>
<tr>
<td>TAVS</td>
<td>Transverse Anastomosis Vascular Stapler</td>
</tr>
<tr>
<td>THVE</td>
<td>Total hepatic vascular exclusion</td>
</tr>
<tr>
<td>UCSF</td>
<td>University of California at San Francisco</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasongraphy</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>VVB</td>
<td>Veno-venous bypass</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Aim of The Work

The aim of this work is to compare outcome of hepatic resection and radiofrequency ablation (RFA) in two groups of patients with a solitary hepatocellular carcinoma (HCC) less than 5 cm in Childs A cirrhotic patients with thoroughing some light on the recent trends in diagnosis and treatment of HCC.
Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancers in the world, with an estimated 500,000 deaths per year (Livot et al., 2003). Advances in diagnostic imaging and widespread application of screening programs in high-risk populations have allowed detection of small HCC, which can be curable by partial hepatic resection (HR), liver transplantation, or local ablation therapies. Out of these, liver transplantation, which offers the potential to both resect the entire potentially tumour-bearing liver and eliminate the cirrhosis, achieves the best results but can be offered only to a minority of patients because of the shortage of donors and high cost (Befeler et al., 2005).

Therefore HR has generally been accepted as the first treatment of choice for HCC in many centres. Nevertheless, the associated cirrhosis carries a high risk of intraoperative hemorrhage and limits the extent of surgery thus increases the risk of postoperative liver failure. So, many nonsurgical ablative methods have been developed for patients with small HCC not eligible for surgery, such as cryoablation, percutaneous ethanol injection, acetic acid injection, radiofrequency ablation (RFA), microwave coagulation and Transcatheter arterial chemoembolization (Huo et al., 2006).

Among these therapies RFA is a promising and recently developed ablation technique. It induces deep thermal injury in hepatic tissue while sparing the normal parenchyma. basic principle includes generation of high-frequency alternating current which causes ionic agitation and conversion to heat, with subsequent evaporation of intracellular water which leads to irreversible cellular changes, including intracellular protein denaturation, melting of membrane lipid bilayers, and coagulative necrosis of individual tumour cells (Bruix et al., 2005).
Cohort studies have shown RFA to give encouraging results in terms of tumor control, with complete tumor ablation rates of 90% to 95% and low local recurrence rate of 5% to 10%. The treatment has also been shown to be safe, with a 3-year survival rate of 62% to 68%. More recently, RFA has been also successfully offered in patients eligible for liver resection or transplantation (Wood et al., 2000).

More recently, RFA has been also successfully offered in patients eligible for liver resection or transplantation (Curley, 2003).
Surgical Anatomy of Liver

Modern liver surgery is derived from the anatomic concepts initiated by Couinaud in 1957 and developed by Ton That Tung in 1962 and Bismuth in 1982. The surgical anatomy of the liver is based on detailed knowledge of its natural divisions, including congenital variants, and comprises morphologic and functional aspects. Complete understanding of the surgical anatomy is essential for any practitioner who intervenes in the liver and biliary tract, whether by open surgery, a laparoscopic approach, or any of the diagnostic or therapeutic percutaneous intrahepatic interventions that are emerging. (*Bismuth and Vibert, 2007*).

A precise knowledge of the anatomy of the liver is an absolute prerequisite to performing surgery on the liver or biliary tree. With the development of hepatic surgery during the past few decades, a greater appreciation for the complex anatomy beyond the misleading minimal external markings has been realized. The days of using the falciform ligament as the only marker of a left and right side of the liver are over, and the anatomic contributions of Couinaud (see later) and the description of the segmental nature of the liver need to be embraced and studied (*Jones and Hardy, 2006*).
Gross Anatomy (morphologic anatomy):

The liver is a solid gastrointestinal organ whose mass (1200-1600g) largely occupies the right upper quadrant of the abdomen. The costal margin coincides with the lower margin and the superior surface is draped over by the diaphragm. Most of the right liver and most of the left liver is covered by the thoracic cage. The liver extends superiorly to the height of the fifth rib on the right and the sixth rib on the left. The posterior surface straddles the inferior vena cava (IVC). A wedge of liver extends to the left half of the abdomen across the epigastrium to lie above the anterior surface of the stomach and under the central and left diaphragm. The superior surface of the liver is convex and is molded to the diaphragm, (Fig1) whereas the inferior surface is mildly concave and extends to a sharp anterior border (Fig 2) (Bismuth, 2007).
Fig (1): Diaphragmatic aspect of the liver illustrating features of the anterior and superior surfaces (Jones and Hardy, 2006).

Fig (2): Porta hepatis and features of the visceral surface of the liver (Bismuth, 2007).
Peritoneal attachment of the liver:

The liver is invested in the peritoneum except for the gallbladder bed, the porta hepatis, and posteriorly on either side of the IVC in two wedge shaped areas (called the *bare area* of the liver to the right of the IVC). The peritoneal duplications on the liver surface are referred to as ligaments. The diaphragmatic peritoneal duplications are referred to as the *coronary ligament*, whose lateral margins on either side are the right and left triangular ligaments (Fig 3). From the center of the coronary ligament emerges the falciform ligament, which extends anteriorly as a thin membrane connecting the liver surface to the diaphragm, abdominal wall, and umbilicus. The ligamentum teres (the obliterated umbilical vein) runs along the inferior edge of the falciform ligament from the umbilicus to the umbilical fissure. The umbilical fissure is on the inferior surface of the left liver and contains the left portal triad. The falciform ligament, the most obvious surface marking of the liver, historically was used to mark the division of the right and left lobes of the liver in early descriptions of hepatic anatomy. On the posterior surface of the left liver, ligamentum venosum (obliterated sinus venosus) running from the left portal vein in the porta hepatis toward the left hepatic vein and the IVC (*Strasberg et al., 2000*).
Fig (3): Anterior view of the liver. The esophagus is pulled upwards from its normal position behind the left lobe to show the peritoneal attachments. All peritoneal edges seen here are attached to the diaphragm (*Strasberg et al.*, 2000).

**Functional Anatomy (Segmental Anatomy)**:

Historically, the liver was divided into left and right lobes by the obvious external landmark of the falciform ligament. Not only was this description oversimplified, but it was also anatomically incorrect in relationship to the blood supply to the liver (Fig 4) (*Botero and Strasberg*, 2002).
Fig (4): Hepatic "true" lobar and segmental divisions (Botero and Strasberg, 2002).

The functional anatomy of the liver is composed of eight segments, each of which is supplied by a single portal triad (also called a pedicle) composed of a portal vein, hepatic artery, and bile duct. These segments are further organized into four sectors that are separated by scissurae containing the three main hepatic veins. The four sectors are even further organized into the right and left liver (Fig 5). This system was originally described in 1957 by Woodsmith and Goldburne as well as Couinaud and defines hepatic anatomy as it is most relevant to surgery of the liver (Bruix et al., 2005).
Liver scissura and fissures (Fig 5&6):

The main scissura contains the middle hepatic vein, which runs in an anteroposterior direction from the gallbladder fossa to the left side of the vena cava and divides the liver into right and left hemi-livers. The line of the main scissura is also known as Cantlie's line. The right liver is divided into an anterior (segments V and VIII) and posterior (segments VI and VII) sector by the right scissura, which contains the right hepatic vein. The right portal pedicle, composed of the right hepatic artery, portal vein, and bile duct, splits into right anterior and posterior pedicles that supply the segments of the anterior and posterior sectors (Kawarada et al., 2004).
Surgical Anatomy of Liver

The left liver has a visible fissure along its inferior surface called the umbilical fissure. The ligamentum teres (containing the remnant of the umbilical vein) runs into this fissure. The falciform ligament is contiguous with the umbilical fissure and ligamentum teres. The umbilical fissure is not a scissura, does not contain a hepatic vein, and in fact, contains the left portal pedicle (triad containing the left portal vein, hepatic artery, and bile duct), which runs in this fissure, branching to feed the left liver. The left scissura runs posterior to the ligamentum teres and contains the left hepatic vein (Blumgart et al., 2007).

Caudate lobe:

The caudate lobe (segment I) is the dorsal portion of the liver and embraces the IVC on its posterior surface and lies posterior to the left portal triad inferiorly and the left and middle hepatic veins superiorly. The main bulk of the caudate lobe is to the left of the IVC, but inferiorly, it traverses between the IVC and left portal triad, where it fuses to the right liver (segments VI and VII). This part of the caudate lobe is known as the right portion or the caudate process. The left portion of the caudate lobe lies in the lesser omental bursa and is covered anteriorly by the gastrohepatic ligament (lesser omentum) that separates it from segments II and III anteriorly (Makuuchi et al., 2006).
The Hepatic Lobes

It is quite confusing when there are many different names for lobes and segments of the liver. For example, what is called "lobectomy" in Europe is often different in meaning from the same term in the United States of America. "Lobectomy" in the United States is equivalent of "hepatectomy" in Europe while "right lobectomy" in Europe is called "right trisegmentectomy" or "extended right lobectomy" in the United States, and "Left lobectomy" in Europe is called "left lateral segmentectomy" in the United States. In Europe the liver is usually described as having eight segments, while it is most often divided into four segments in the United States. In Japan and other countries, European segments are called "subsegments" to avoid the confusion. So-called (used to be so-called) anatomical right and left lobe are not "true" right and left lobes founded upon an embryologic or truly morphological basis (Iwatsuki et al, 1989) table (1).

Table (1): Liver anatomy classification (Mazziotti and Cavallari, 1997).

<table>
<thead>
<tr>
<th>Segments</th>
<th>Couinaud's Classification</th>
<th>Healey's Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3</td>
<td>Left lobe</td>
<td>Left lateral segment</td>
</tr>
<tr>
<td>4</td>
<td>Left Paramedian sector</td>
<td>Left medial segment</td>
</tr>
<tr>
<td>2,3,4</td>
<td>Left hemiliver</td>
<td>Left lobe</td>
</tr>
<tr>
<td>5,8</td>
<td>Right medial sector</td>
<td>Right anterior segment</td>
</tr>
<tr>
<td>6,7</td>
<td>Right lateral sector</td>
<td>Right posterior segment</td>
</tr>
<tr>
<td>5,6,7,8</td>
<td>Right hemiliver</td>
<td>Right lobe</td>
</tr>
<tr>
<td>1</td>
<td>Caudate (Spigelian)lobe</td>
<td>Caudate lobe</td>
</tr>
</tbody>
</table>
Portal Vein (Fig 5&6):

The portal vein provides about 75% of hepatic blood flow, and although it is postcapillary and largely deoxygenated, its large-volume flow rate provides 50% to 70% of the liver's oxygenation (Launois et al., 2005).

Intrahepatic distribution of the portal vein:

The portal vein forms behind the neck of the pancreas at the confluence of the superior mesenteric vein and the splenic vein at the height of the second lumbar vertebra. The length of the main portal vein ranges from 5.5 to 8 cm, and its diameter is usually about 1 cm. Its formation behind the neck of the pancreas, the portal vein runs behind the first portion of the duodenum and into the hepatoduodenal ligament, where it runs along the right border of the lesser omentum, usually posterior to the bile duct and hepatic artery (Kawarada et al., 2004).

The portal vein divides into main right and left branches at the hilum of the liver. The left branch of the portal vein runs transversely along the base of segment IV and into the umbilical fissure, where it gives off branches to segments II and III and feedback branches to segment IV. The left portal vein also gives off posterior branches to the left side of the caudate lobe. The right portal vein has a short extrahepatic course and usually enters the substance of the liver, where it splits into anterior and posterior sectoral branches (Blumgart et al., 2007).
Fig. (6): Exploded diagrammatic sketch of the liver. The middle hepatic vein runs within the main portal fissure (Cantlie's line), which separates the left liver (segments 2 to 4) from the right liver (segments 5 to 8). The hepatic veins are distributed on an intersegmental basis. VC, vena cava; R, right; M, middle; L, left hepatic veins, and 1, caudate lobe (DeMatteo et al., 2002).

Hepatic Artery (Fig 7&8):

Embryologically, there are three hepatic arteries: A left artery arising from the left gastric artery, a middle from the celiac axis and a right from SMA. Usually, the left and right disappear, leaving the embryologic middle branch from the celiac axis. In 17% of cases, the right hepatic artery originating from SMA may persist in addition to replace the right branch of main hepatic artery and in 23% of cases the left hepatic artery arises from the left gastric artery (Fig 7) (Bismuth, et al., 1998).
The hepatic artery, representing high flow oxygenated systemic arterial flow, provides about 25% of the hepatic blood flow and 30% to 50% of its oxygenation. A number of smaller perihepatic arteries derived from the inferior phrenic and the gastroduodenal arteries also supply the liver. These vessels are important sources of collateral blood flow in the event of occlusion of the main hepatic arterial inflow \( \text{(Skandalakis et al., 2006)} \).
Fig. (8): Diagram to show the intrahepatic distribution of the hepatic artery. The "returning loop" of the left branch at the junction of medial and lateral segments. It is liable to injury here during left lateral segmentectomy (Skandalakis et al., 2006).

Course of the hepatic artery:

The celiac trunk originates directly off the aorta just below the aortic diaphragmatic hiatus and gives off three branches: the splenic artery, the left gastric artery, and the common hepatic artery (Gruttadauria et al., 2006).

The common hepatic artery passes forward and to the right along the superior border of the pancreas and runs along the right side of the lesser omentum, where it ascends toward the hepatic hilum lying anterior to the portal vein and to the left of the bile duct (Jones and Hardy, 2006).
At the point that the common hepatic artery begins to head superiorly toward the hepatic hilum, it gives off the gastroduodenal artery, followed by the supraduodenal artery and then the right gastric artery. The common hepatic artery beyond the takeoff of the gastroduodenal artery is called the **proper hepatic artery** and divides into right and left branches at the hilum. The left hepatic artery heads vertically toward the umbilical fissure to supply segments I, II, and III (*Launois et al.*, 2005).

The left hepatic artery usually gives off a middle hepatic artery branch that heads toward the right side of the umbilical fissure and supplies segment IV (Fig 8). The right hepatic artery usually runs posterior to the common hepatic bile duct and enters Calot's triangle (bordered by the cystic duct, common hepatic duct, and the liver edge), where it gives off the cystic artery to supply the gallbladder and then continues into the substance of the right liver (*Strasberg et al.*, 2000).

**Hepatic Veins (Fig 9):**

The three major hepatic veins drain from the superior and posterior surface of the liver directly into the IVC. The right hepatic vein runs in the right scissura (between the anterior and posterior sectors of the right liver) and drains most of the right liver after a short (1-cm) extrahepatic course into the right side of the IVC. The left and middle hepatic veins usually join intrahepatically and enter the left side of the IVC as a single vessel, although they may drain separately. The left hepatic vein runs in the left scissura (between segments II and III) and drains segments II and III, and the middle hepatic vein runs in the portal
scissura (between segment IV and the anterior sector of the right liver) draining segment IV and some of the anterior sector of the right liver (Hanazaki et al., 2001).

Fig. (9): Diagram of the intrahepatic distribution of the hepatic veins. These veins lie between lobes and segments rather than within them (Hanazaki et al., 2001).

**Biliary System:**

**Intrahepatic bile ducts:**

The intrahepatic bile ducts are terminal branches of the main right and left hepatic ductal branches that invaginate Glisson's capsule at the hilum along with corresponding portal vein and hepatic artery branches, forming the portal triads (Casavilla et al., 1997).
The left hepatic bile duct drains segments I, II, III, and IV, (left liver). The intrahepatic ductal branches of the left liver join to form the main left duct at the base of the umbilical fissure, where the left hepatic duct courses transversely across the base of segment IV to join the right hepatic duct at the hilum (Nakagohri et al., 2003).

The right hepatic duct drains the right liver and is formed by the joining of the anterior sectoral duct (draining segments V and VIII) and the posterior sectoral duct (draining segments VI and VII). The posterior sectoral duct runs in a horizontal and posterior direction, whereas the anterior sectoral duct runs vertically. The short right hepatic duct meets the longer left hepatic duct, forming the confluence anterior to the right portal vein, constituting the common hepatic duct (Mayer et al., 1997).

Common hepatic duct:

The common hepatic duct drains inferiorly, and below the takeoff of the cystic duct is referred to as the common bile duct. The common bile or hepatic duct runs along the right side of the hepatoduodenal ligament (free edge of the lesser omentum) to the right of the hepatic artery and anterior to the portal vein. The common bile duct continues inferiorly behind the first portion of the duodenum and into the head of the pancreas in an inferior and slightly rightward direction. The intrapancreatic distal common bile duct then joins with the main pancreatic duct (of Wirsung), to enter the second portion of the duodenum through the major papilla of Vater. At the choledochoduodenal junction, a complex muscular complex known as the sphincter of Oddi regulates bile flow and prevents reflux of duodenal contents into the biliary tree (Lieser et al., 2004).
**The Gallbladder:**

The gallbladder is a biliary reservoir that lies against the inferior surface of segments IV and V of the liver, usually making an impression against it. A peritoneal layer covers most of the gallbladder except for the portion adherent to the liver. Where the gallbladder is adherent to the liver, the gallbladder is composed of a fundus, body, infundibulum, and neck that ultimately empties into the cystic duct. The fundus usually projects just slightly beyond the liver edge anteriorly and when folded on itself is described as a *Phrygian cap*. Continuing toward the bile duct, the body of the gallbladder is usually in close proximity to the second portion of the duodenum and the transverse colon. The infundibulum (or Hartmann's pouch) hangs forward along the free edge of the lesser omentum and can fold in front of the cystic duct. The portion of gallbladder between the infundibulum and the cystic duct is the neck of the gallbladder. Most commonly, the cystic duct joins the hepatic duct to form the common bile duct (*Bismuth, 2007*).
Epidemiology of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and one of the most common malignancies worldwide, accounting for more than 1 million deaths annually (El-Serag, 2004).

Hepatocellular carcinoma is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death (Llovet et al., 2004)

Geographic distribution of HCC:

The geographic distribution of HCC is clearly related to the incidence of hepatitis (B & C) viruses infection. The highest incidence of disease (>10-20 per 100,000) is found in Southeast Asia and tropical Africa, and the lowest incidence (1-3 per 100,000) is found in Australia, North America, and Europe. In high incidence areas, rates are variable. For example, Taiwan has an incidence of 150 per 100,000, whereas Singapore has an incidence of 28 per 100,000. Epidemiologic evidence strongly suggests that HCC is largely related to environmental factors (Fig 10). (Bosch and Garcia-Pagan, 2005).

Whites living in high prevalence areas tend to have a low incidence of HCC. This is likely related to the continuation of the lifestyle and environment of their home country (Collier and Sherman, 2006). Recent publications have noted a significant rise in the incidence of HCC in the United States and other Western countries during the past 30 years. The explanation of this rising incidence is not understood, but emergence of hepatitis C virus (HCV) infection (El-Serag, 2004).
HCC is now a common malignancy in Egypt, which usually develops on top of cirrhosis of viral origin (Abdel-Wahab et al., 2000). Egyptian studies carried on HCC presumed an upward trend among chronic liver disease patients (El-Zayadi et al., 2001).

![Geographic distribution of HCC.](Shariff et al., 2009)

**Fig (10):** Geographic distribution of HCC. (Shariff et al., 2009).

**Sex distribution:**

Hepatocellular carcinoma is more common in males than females with the ratio 4:1; this ratio varies widely according to the geographic distribution and may reach up to 8:1. World-Wide hepatocellular carcinoma is the seventh most common form of cancer in men and the ninth in women. (Sherlock & Dooley, 1993).

**Age distribution:**

The peak age incidence of hepatocellular carcinoma varies from 40 years in southern Africa, 40-60 years in Asia and 80 years in the UK (Okuda, et al., 1991).
Risk Factors of Hepatocellular Carcinoma

Risk factors for development of HCC include:

1. Hepatic viral infections,
2. Environmental exposures,
3. Chronic alcohol abuse,
4. Smoking,
5. Genetic metabolic diseases,
6. Cirrhosis,
7. Others:
   - Oral contraceptive pills
   - NASH: Nonalcoholic steatohepatitis (Nonalcoholic Fatty Liver Disease, Obesity & Diabetes Mellitus) (Fig 11).

Fig (11): Risk factors for development of HCC. *(Shariff et al, 2009)*.
**Hepatic viral infection:**

Overall, 75% to 80% of HCC cases are related to hepatic viral infections (HBV & HCV). What is also clear from research is that the development of HCC is a complex and multistep process that involves any number of these risk factors (Bruix and Llovet, 2002).

**(A) Hepatitis B viral infection:**

Many years of research have documented a clear association between persistent HBV infection and the development of HCC. Other evidence is that the geographic areas high in HBV infection have a high rate of HCC (Izzo et al., 1998).

**(B) Hepatitis C viral infection:**

HCV has recently been discovered to be a major cause of chronic liver disease in Japan, Europe, and the United States, where there is a relatively low rate of HBV infection. Antibodies to HCV are found in 76% of patients with HCC in Japan and Europe and in 36% of patients in the United States (Gebo et al., 2005).

HBV and HCV infection are both independent risk factors for the development of HCC but probably act synergistically when an individual is infected with both viruses. Although the natural history of HCV infection is not completely understood, it appears to be one of the chronic infections with a benign early course but with ultimate development of cirrhosis and HCC (Izzo et al., 2010).
HCV is an RNA virus that does not integrate into the host genome, and therefore, the pathogenesis of HCV-related HCC may be more related to chronic inflammation and cirrhosis rather than direct carcinogenesis (Figueras et al., 2001).

**Liver cirrhosis:**

The true relationship of cirrhosis and HCC is difficult to ascertain, and suggestions of causation remain speculative. Cirrhosis is not required for the development of HCC, and HCC is not an inevitable result of cirrhosis. The relationship of cirrhosis and HCC is further complicated by the fact that they share common associations. Furthermore, some associations (e.g., HBV infection, hemochromatosis) are associated with higher risk for HCC, whereas others (e.g., alcohol, primary biliary cirrhosis) are associated with a lower risk for HCC. Cirrhotic livers with higher DNA replication rates are associated with the development of HCC (Ercolani et al., 2003).

**Chronic alcohol abuse:**

Chronic alcohol abuse has been associated with a significant risk for HCC, and there may be a synergistic effect with HBV and HCV infection. Alcohol causes cirrhosis but has never been shown to be directly carcinogenic to hepatocytes (Gebo et al., 2005).
Aflatoxin exposure:

Aflatoxin acts as a carcinogen and increases the risk for HCC. The offending fungi grow on grains, peanuts, and food products in tropical and subtropical regions, and intake of contaminated foods results in aflatoxin exposure (Figueras et al., 2001).

Chemical exposures:

A variety of chemicals have been implicated as carcinogens related to HCC and include nitrites, hydrocarbons, solvents, pesticides, and vinyl chloride. Thorotrast (colloidal thorium dioxide) is an angiographic medium that was used in the 1930s that emits high levels of long-lasting radiation and has been associated with hepatic fibrosis, angiosarcoma, cholangiosarcoma, and HCC (Izzo et al., 1998).

Inherited metabolic liver diseases:

Associations with inherited metabolic liver diseases, such as hereditary hemochromatosis, $\alpha_1$-antitrypsin deficiency, and Wilson's disease, have also been implicated as risk factors for HCC (Gebo et al., 2005).

Cigarette smoking:

Cigarette smoking has been linked to the development of HCC, but the evidence is not consistent (Bruix and Llovet, 2002).
Obesity And Diabetes Mellitus:

Epidemiological studies have shown that obesity is a risk factor for hepatocellular carcinoma. Similar studies further indicate that diabetes is also a major risk factor. Both obesity and diabetes are frequently associated with nonalcoholic fatty liver disease, and case reports have shown progression of nonalcoholic fatty liver disease to cirrhosis and hepatocellular carcinoma.

The mechanism most likely involves replicative senescence of steatotic mature hepatocytes and compensatory hyperplasia of progenitor (oval) cells as a reaction to chronic injury due to ongoing nonalcoholic steatohepatitis and resultant hepatic fibrosis. Growth factors associated with chronic inflammation, type 2 diabetes, and DNA mutations as a result of lipid peroxidation probably play significant roles in clonal expansion and hepatocellular carcinoma progression.

It remains unclear whether cirrhosis is a prerequisite for the development of hepatocellular carcinoma or whether hepatocellular carcinoma can develop in fatty liver in the absence of cirrhosis. However, well-documented case reports suggest that most cases of hepatocellular carcinoma arise in the setting of nonalcoholic steatohepatitis with cirrhosis (Caldwell et al., 2004).

Oral contraceptive pills:

The use of oral contraceptive pills and risk for HCC development is inconclusive. There is significant increase in HCC risk with longer duration of exposure of oral contraceptives (>5 years). (Hassan and Kaseb, 2011).
Pathology of HCC

Growth patterns and grading of HCC.

Hepatocellular carcinoma can be classified into three different growth patterns, and these growth patterns have a much greater influence than does histologic grade on resectability and therefore, on long-term outcome.

1. The hanging type of tumor is attached to the normal liver by a small vascular stalk, even if the tumor is large. This type is easily excised with little loss in functional parenchyma.

2. The pushing type generally is well demarcated and often encapsulated by a fibrous capsule. This type of tumor displaces normal vasculature rather than infiltrates and invades the major vessels. It is often resectable, even when tumor bulk is substantial.

3. The infiltrative type has a very indistinct tumor-liver interface and tends to exhibit a much greater degree of vascular infiltration and invasion, even when the tumor is small. Excising the infiltrating type often is complicated by positive margins. (Yuman, et al., 2001).

WHO Classification:

Hepatocellular carcinoma is classified into five subtypes according to the histologic pattern: Trabecular type (plate like), pseudoglandular (acinar), compact, scirrhouos, and fibrolamellar carcinoma. The trabecular and pseudoglandular patterns are the most common in well to moderately differentiated hepatocellular carcinomas. The compact pattern is generally observed in poorly differentiated hepatocellular carcinoma.
The scirrhous pattern is characterized by abundant fibrous stroma separating cords of tumor cells, and it is often seen following radiation, chemotherapy, or infarction. *(Ishak et al., 1997)*.

**Fibrolamellar Carcinoma:**

Fibrolamellar carcinoma (FLC) was first described by Edmonson in 1956. It is a rare hepatic malignancy, comprising less than 1% of primary liver malignancies in a US population-based study. The histologic appearance of FLC is distinctive, consisting of deeply eosinophilic malignant hepatocytes surrounded by thick fibrous bands arranged in a lamellar-like fashion. Radiographically, the tumors are hyper-vascular and tend to be large, be calcified, and have a central scar, all distinct differences from conventional HCC (Table 2). Many consider it a variant of HCC, though the epidemiology, clinicopathologic factors, and prognosis differ widely from HCC. *(Ichikawa et al., 1999)*.

FLC is largely tumors of youth and young adulthood. The median age of patients with FLC is on the order of 25 years, far younger than conventional HCC. *(Moreno-Luna et al., 2005)*

**Table (2):** Differences between fibrolamellar carcinoma and traditional HCC. *(Ichikawa et al., 1999).*

<table>
<thead>
<tr>
<th>Fibrolamellar</th>
<th>Traditional HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient related</td>
<td>Young age</td>
</tr>
<tr>
<td></td>
<td>Lack fibrosis</td>
</tr>
<tr>
<td></td>
<td>Better survival</td>
</tr>
<tr>
<td>Tumor related</td>
<td>Central scar</td>
</tr>
<tr>
<td></td>
<td>Typically solitary</td>
</tr>
<tr>
<td></td>
<td>Higher resection rate</td>
</tr>
</tbody>
</table>
Grading:

According to histological grade, HCC is classified into Well differentiated, Moderately differentiated, Poorly differentiated, and undifferentiated types (Fig 12). (Morimistu et al., 1995).

1) Well differentiated HCC:

This is the most commonly seen in small, early stage tumors less than 2 cm in diameter and is rare in advanced tumors. The lesions are composed of cells with minimal atypia and increased nuclear/cytoplasmic ratio (N/C ratio) in a thin trabecular pattern, with frequent pseudoglandular or acinar structures and frequent fatty changes. In most tumors larger than 3 cm in diameter, well differentiated carcinoma is observed only in the periphery.

2) Moderately differentiated HCC:

The Moderately differentiated type is the commonest in tumors larger than 3 cm in diameter and is characterized by tumor cells arranged in trabeculae of three or more cells in thickness. Tumor cells have abundant eosinophillic cytoplasm and round nuclei with distinct nucleoli. A pseudoglandular pattern is also frequent, and pseudoglands frequently contain bile or proteinaceous fluid.
3) Poorly differentiated HCC:

This proliferates in a solid pattern without distinct sinusoid like blood spaces, and only slit like blood spaces, and only slit like blood vessels are observed in large tumor nests. Neoplastic cells show an increased N/C ratio and frequent pleomorphism, including bizarre giant cells. Poorly differentiated HCC is extremely rare in small early stage tumors.

4) Undifferentiated HCC:

Undifferentiated HCCs are composed of tumor cells with little cytoplasm and short spindle-shaped or round nuclei. They grow in a solid or medullary pattern. (Morimistu et al., 1995).
Fig (12): Histological differentiation of hepatocellular carcinoma showing cytological and architectural features. *(Skawran et al., 2008.)*

(a) Well-differentiated hepatocellular carcinoma is defined by nuclei shape, which is very similar to normal hepatocytes.

(b) Moderately differentiated carcinoma reveals a heterogeneous pattern with respect to cytology of nuclei and architectural pattern.

(c) In moderate-to-poorly differentiated hepatocellular carcinoma, prominent nucleoli are seen in the nuclei; the shape of the nuclei and membrane is irregular. The trabecular pattern is also disturbed in a prominent way, making recognition of trabecular structures difficult.

(d) In dedifferentiated hepatocellular carcinoma, nuclei have a bizarre and highly irregular shape, and lose their architectural pattern, making it difficult to separate these carcinomas from dedifferentiated carcinomas of other s
Staging of hepatocellular Carcinoma

1. **TNM classification** *(Francis, et al., 1999)*:

   **Primary tumor (T):**
   
   1. **Tx:** -primary tumor cannot be assessed.
   2. **To:** -No evidence of primary tumor.
   3. **T1:** -solitary tumor 2cm or less in greatest dimension without vascular invasion.
   4. **T2:**
      - solitary tumor 2cm or less in greatest dimension with vascular invasion;
      - or multiple tumors limited to one lobe, none more than 2cm in greatest dimension without vascular invasion;
      - or a solitary tumor more than 2cm in greatest dimension without vascular invasion.
   5. **T3:**
      - solitary tumor more than 2cm in greatest dimension with vascular invasion;
      - or multiple tumors limited to one lobe, none more than 2cm in greatest dimension, with vascular invasion;
      - or multiple tumors limited to one lobe, any more than 2cm in greatest dimension, with or without vascular invasion.
   6. **T4:**
      - Multiple tumors in more than one lobe
      - or tumor (s) involving a major branch of portal or hepatic vein (s)
      - or invasion of adjacent organs other than the gall-bladder
      - or perforation of the visceral peritoneum.
Regional lymph nodes (N):

- Nx: Regional lymph nodes cannot be assessed.
- No: No regional lymph nodes metastasis.
- N1: Regional lymph node metastasis.

Note: The regional lymph nodes are the hilar (i.e. those in the hepato-duodenal ligament, hepatic and periportal nodes). Regional lymph nodes also include those along the inferior vena cava, hepatic artery, and portal vein. Any lymph node involvement beyond these nodes is considered distant metastasis and should be coded as M1.

Distant metastasis (M):

- Mx: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis. (Table 3). (Francis, et al., 1999).
Table (3): The American Joint committee on cancer (AJCC) stage grouping (Francis, et al., 1999).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1, No, Mo</td>
</tr>
<tr>
<td>II</td>
<td>T2, No, Mo</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3, No, Mo</td>
</tr>
<tr>
<td>III B</td>
<td>T1, N1, Mo</td>
</tr>
<tr>
<td></td>
<td>T2, N1, Mo</td>
</tr>
<tr>
<td></td>
<td>T3, N1, Mo</td>
</tr>
<tr>
<td>IVA</td>
<td>T4, Any N, Mo</td>
</tr>
<tr>
<td>IV B</td>
<td>Any T, any N, M1</td>
</tr>
</tbody>
</table>

For the purposes of treatment, patient with liver cancer are grouped as localized resectable, localized unresectable or advanced disease. These groups are described with the following TNM correlations. (Francis, et al., 1999).

1. **Localized resectable:**

   (T1, T2, T3, and selected T4, No; Mo)

   This type of liver cancer confined to a solitary mass in a portion of the liver that allows the possibility of complete surgical removal of the tumor with margin of normal liver. Liver function tests are usually normal or minimally abnormal, and there should be no evidence of cirrhosis or chronic hepatitis. Only a small percentage of liver cancer patient will prove to have such localized resectable disease. (Venook, 1994).
2. Localized unresectable:

(Selected T2, T3, and T4, No; Mo)

This type of cancer appears to be confined to the liver, but surgical resection of the entire tumor is not possible despite a localized mass because of location within the liver or concomitant medical conditions. (Such as cirrhosis). Patients with locally unresectable fibrolamellar variant hepatomas may be considered for liver transplantation. For other patients, chemoembolization may be an option. (Iwatsuki, et al., 1999).

3. Advanced (Any T, N1 or M1):

Advanced liver cancer is cancer that is present in both lobes of the liver or has metastasized to distant sites. Multifocal disease in the liver is common, particularly when cirrhosis or chronic hepatitis is present (Tanaka, et al., 1998).

II. Clinical Staging:

It is well known that clinical stage is the most important factor influencing on the prognosis of HCC patients. The most widely used prognostic tools are The Child-Pugh Classification, The Okuda Classification, and The Cancer Of The Liver Italian Program (CLIP) Score. The Barcelona Clinic Liver Cancer (BCLC) Staging have been recently described. (Cillo et al., 2004)
• **The Child-Pugh Classification:**

The Child-Pugh score was not developed for HCC patients. It considers only features related to liver function and does not include cancer parameters. In western countries, the Child–Pugh (CP) classification, which was originally designed to estimate the risk of cirrhotic patients undergoing portocaval shunt surgery for portal hypertension, has traditionally been used to evaluate the hepatic function. Usually only patients with Child–Pugh class A disease are considered good candidates for hepatectomy (Table 4). *(Pugh et al., 1973).*

Table (4): Child-Pugh's *(Pugh et al., 1973).*

<table>
<thead>
<tr>
<th>Encephalopathy grade</th>
<th>None</th>
<th>1 and 2</th>
<th>3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Serum bilirubin, mg/dL</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Prothrombin time, seconds (prolonged)</td>
<td>1-4</td>
<td>4-6</td>
<td>&gt;6.0</td>
</tr>
</tbody>
</table>

(Child A → 5, 6) (Child B → 7, 9) (Child C → 10, 15)
The Okuda Classification:

The Okuda scheme, proposed in 1985, was derived from an analysis of 850 Japanese patients who were treated with a range of surgical and non-surgical therapies. In the Okuda system, patients are stratified based on the presence or absence of four factors: tumor involving >50% of the liver, ascites, serum albumin <3 g/dL, and serum bilirubin >3 mg/dL. Stage I disease was defined as having none of these features, Stage II as having one or two of these features, and Stage III as having three or four of these features. Although the Okuda staging system was once the most widely used, it has now fallen out of favor. There are two main criticisms of this system. First, it was derived in a cohort of patients with relatively advanced HCC and as such is less useful for prognostic discrimination at earlier stages of the disease. Second, it includes only one tumor-specific prognostic factor and therefore treats a wide range of tumors (all tumor sizes <50% of liver volume, solitary or multifocal, and with or without vascular invasion) as having comparable prognoses. Its usefulness in patients who do not have advanced disease is therefore limited (Table 5). (Okuda et al., 1985).

Table (5): Okuda classification (Okuda et al., 1985).

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Ascites</th>
<th>Albumin</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50%</td>
<td>&lt;50%</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Score</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

(Stage 1→ All - ve) (Stage 2→ 1 or 2 + ve) (Stage 3→ 3 or 4 + ve)
The Cancer Of The Liver Italian Program (CLIP) Score:

The CLIP score is able to predict survival better than the Okuda or TNM staging system, accurately identify patients with different prognoses, particularly in the early phases of HCC (Table 6) . (Lui et al., 1999).

Table (6) : Cancer of the Liver Italian Program (CLIP) score. (Lui et al., 1999).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Child–Pugh grade</td>
<td>A</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td>Solitary and ≤50%</td>
</tr>
<tr>
<td>Serum α-fetoprotein</td>
<td>&lt;400 ng/mL</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Absent</td>
</tr>
</tbody>
</table>

The Barcelona Clinic Liver Cancer (BCLC) Staging:

The BCLC staging system was constructed based on the results of several cohort and Randomized Controlled Trial (RCTs) . This classification uses variables related to tumor stage, liver functions, and physical status and links them with a treatment algorithm (Fig 13) . (Llovet et al., 1999).
The BCLC staging showed the best interpretation of the survival distribution in an HCC population comprising a large proportion of tumors treated with potentially radical therapies (resection and percutaneous ablation). (Cillo et al., 2004).
Spread and prognosis:

Hepatocellular carcinoma has a characteristic tendency for intravascular spread and the involvement of major hepatic veins and of the portal vein. HCC is characterized also by the much less common direct spread into the hepatic and common bile ducts. The tumor seldom breaches Glisson's capsule and growth into adjacent structures or the omentum through the diaphragm or the abdominal wall. Dissemination throughout the peritoneal cavity is a rare condition. There are more commonly lymphatic spread to the lymph nodes in the porta hepatis, around the pancreas and the celiac axis. Haematogenous spread occurs less often and most of all to the lung; other sites include adrenals, stomach, heart, pancreas, kidney, spleen, ovary and bone. In two studies from North America improved survival was related to age less than 50 years, female gender, tumors of better histological grade, low mitotic index and no vascular invasion, and the absence of cirrhosis. The best prognosis is obtained in asymptomatic cases detected by screening of individuals at high risk utilizing ultra sound examination and determination of serum AFP level. (Anthony, 2002).
Diagnosis of Hepatocellular Carcinoma

Clinical Presentation:

Most commonly, patients presenting with HCC are men 50 to 60 years of age who complain of right upper quadrant abdominal pain, weight loss and have a palpable mass (Testa et al., 2000).

In countries endemic for HBV and HCV infections, presentation at a young age is common and probably related to childhood infection (Chen et al., 2003).

Unfortunately, in unscreened populations, HCC tends to present at a late stage because of the lack of symptoms in early stages. Presentation at this advanced stage is often with a vague right upper quadrant abdominal pain that sometimes radiates to the right shoulder. Nonspecific symptoms of advanced malignancy such as anorexia, nausea, lethargy, and weight loss are common (Tanaka et al., 2000).

Another common presentation is rapidly progressive hepatic decompensation in patient with known liver cirrhosis, examination of this patient reveals, physical signs of cirrhosis and liver cell failure such as:

- Pallor
- Mentality disturbance (hepatic-coma) and hepatic encephalopathy.
- Jaundice.
- Foetor hepaticus.
- Flapping tremors.
- Spider naevi (Fig 14).
- Gynaecomastia (Fig 15).
- Ascites (Fig 16).
- Caput nedusa.
- Shrunken liver ± splenomegally (Tanaka et al., 2000).

**Fig (14):** Spider naevi (Blumgart et al., 2007).

**Fig (15):** Gynecomastia due to liver cell failure (Blumgart et al., 2007).
Fig (16): Hepatosplenomegally with ascites (Blumgart et al., 2007).

Another presentations are manifestations of portal hypertension such as bleeding oesophageal varices, splenomegally and secondary haemorrhoids (Chen et al., 2003).

The tumor may invade the hepatic veins lead to hepatic veins occlusion (Budd-chiari syndrome) manifested by abdominal pain, vomiting, tender hepatomegally ascites and mild jaundice (Bruix et al., 2005).

Malignant obstructive jaundice is a common presentation of HCC the patient presents with gradual onset, progressive course and short duration of deep jaundice, with low grade fever, weight loss and even metastases, by examination the patient has bradycardia, cachexia, shrunken liver, hepatomegally, enlarged palpable gall bladder (courvoisier low), splenomegally and palpable liver mass may be felt (Iwatsuki et al., 1999).
Less than 1% of cases of HCC present with a paraneoplastic syndrome, most commonly hypercalcemia, hypoglycemia, and erythrocytosis (Testa et al., 2000).

Small, incidentally noted tumors are becoming a more common presentation because of the knowledge of specific risk factors, screening programs for diagnosed HBV or HCV infection, and the increasing use of high-quality abdominal imaging (Yang et al., 2002).

**Investigations for HCC:**

**Radiologic Evaluation of the Liver:**

**Abdominal ultrasound:**

Transcutaneous ultrasound is frequently the first radiologic evaluation performed on the liver (Abbitt, 2002). Ultrasound is an excellent test for identifying the echo-texture of the liver that can suggest the degree of cirrhosis, cystic and solid characteristics of tumors can be delineated (Fig 17). Ultrasonography is used as a screening or follow-up evaluation tool in patients with liver tumors, because it is a readily available and relatively inexpensive technology. Ultrasonography is commonly used in programs that screen high-risk populations for the development of hepatocellular carcinoma (HCC). Ultrasonography has been shown to be superior to serum alpha-fetoprotein (AFP) measurement to detect early HCC in patients who suffer from chronic viral hepatitis (Tong et al., 2001).
**Fig (17):** Small nodule measuring less than 2 cm located in the right lobe (arrow). The nodule is heterogeneous and appears as a thin hypoechoic capsule. Fine-needle aspiration biopsy established the diagnosis of HCC. Early detection of this small tumor allows effective therapy to be initiated *(Harisinghani, 2000).*

The development of new ultrasound technologies including microbubble contrast agents and multi-dimensional imaging may increase the utility of ultrasound as a screening test for malignant tumors, such as HCC. Many of these agents are taken up by cells of the reticuloendothelial system in the liver, and the microbubble contrast agents increase the visibility of HCC. Initial studies of these agents suggest that the sensitivity of ultrasound to detect HCC can be improved and the mean size of the smallest lesions detected is reduced to less than 1 cm *(Blomley et al., 2001).*

Doppler ultrasound, even in the absence of contrast agents, is effective in determining the patency and flow direction of all major hepatic blood vessels, and it can also evaluate the tumor vascularity *(Fuhrman et al., 2000).*
Intraoperative ultrasonography (IOUS) has become the gold standard against which all other diagnostic imaging modalities are compared to detect the number, extent, and association of tumors with intrahepatic blood vessels. IOUS can be performed laparoscopically or during laparotomy (*John et al., 1994*).

Placement of the probe directly on the surface of the liver enhances discrimination and sensitivity. Laparoscopy provides the additional advantage of a visual inspection to exclude the presence of extrahepatic disease on the peritoneal surfaces in the abdominal cavity. Laparoscopic evaluation and laparoscopic ultrasonography have reduced the rate of unwarranted exploratory laparotomies, and thereby increased the proportion of patients who undergo successful hepatic resection at the time of laparotomy (*Jarnagin et al., 2002*).

Like IOUS, laparoscopic ultrasonography detects small metastatic or primary liver tumors not visualized on preoperative CT scans or MRI studies (*Fuhrman et al., 2000*).

Prior to proceeding with liver resection for malignancy, all patients should undergo IOUS as a way of excluding the presence of smaller lesions not detected by preoperative studies. IOUS also can be used to map the line of resection as it relates to relevant vascular structures, in order to avoid and anticipate possible sources of bleeding (Fig 18). IOUS is necessary for intraoperative image-guided procedures such as biopsy and radiofrequency ablation (RFA) (*Blomley et al., 2001*).
**Diagnosis of HCC**

**Fig (18):** (a) The portal branch to segment 7 (P7) is visualized at IOUS on the left and the surgeon’s finger is positioned (F), and P7 is compressed on the right (arrow); (b) the hepatic ischemic area generated by compression with the surgeon’s finger and probe (P), which corresponds to the area to be resected is well evident on the liver surface (arrows); (c) the cut surface at the end of the segment 7 segmentectomy. *(Torzilli et al., 2009).*

**Computed Tomography Scan:**

Modern helical CT scans are highly sensitive at discrimination and quantitation of lesions in the liver. Lesions can be characterized as solid or cystic and the enhancement characteristics can be evaluated during the arterial, portal, and delayed phases *(Harisinghani and Hahn, 2002).*

**Fig (19):** Contrast-enhanced CT scan demonstrating multifocal hepatocellular carcinoma. The left portal vein is invaded and expanded by tumor *(Harisinghani, 2000).*

Three-dimensional reconstructions are useful in preoperative
planning, assessment of hepatic inflow, outflow blood vessels, and measurement of liver volume, which is useful in both resective surgery and living donor transplantation (Fig 19). Dual- and triple-phase intravenous contrast helical CT scan is more accurate than standard CT in detecting HCC. Helical CT can detect HCC small than 2cm and remains one of the preferred method for distinguishing HCC from macroregenerative nodules among patients with liver cirrhosis (*Rode et al.*, 2005).

**Magnetic Resonance Imaging:**

MRI scans are highly accurate than helical CT in detecting HCC, and in distinguishing HCC from macroregenerative nodules. Contrast enhancement provides an evaluation of vascular enhancement similar to CT (Fig 20), but MRI allows for better differentiation Magnetic resonance venography is a very sensitive technique for confirming extrahepatic portal vein thrombosis (*Rode et al.*, 2005).

![Fig (20):](image)

Fig (20): (A) MRI depicts a small nodule with arterial enhancement after contrast administration. (B) The nodule exhibits washout of the contrast material in the venous phase. This is the characteristic pattern of HCC (arrow) (*Harisinghani, 2000*).
**Positron Emission Tomography (PET) Scan:**

The conventional tools to evaluate primary HCC and liver metastases include liver blood tests, abdominal US, CT and MRI. With the increased availability of PET, more institutions performed FDG PET scan to evaluate either primary or metastatic lesions of liver. Fluoro-2-deoxy-D glucose positron emission tomography (FDG PET) is considered to be a very useful imaging technique for the diagnosis, staging, and therapy monitoring of HCC. *(Siggelkow et al., 2003).*

However, the detection of the primary liver tumor, hepatocellular carcinoma, by using FDG PET is still controversial owing to its poor sensitivity. But FDG-PET appears to be a valuable method for histological grading of HCC as well as for monitoring the effect of therapy and tumor viability. *(Chen et al., 2008).*

**Background and Aims:**

Hepatocellular carcinoma, HCC, is a common malignant complication to liver cirrhosis. Early diagnosis is important, but difficult because of difficulties in distinguishing benign cirrhotic liver tissue from malignant tissue using common diagnostic imaging modalities (e.g. MRI, CT, and ultrasound). The aim is to study the feasibility of imaging HCC by PET after injection of the hepatocyte-specific tracer:

- [18F]fluoro-2-deoxy-galactose (FDGal): Galactose is very specifically taken up by hepatocytes and an increased uptake is expected in malignant cells.
- [18F]fluoro-2-deoxy-glucose (FDG): is widely used in oncology to
detect malignant tissue but for HCC it only detects about 2/3 of the nodules.

The uptake of FDG in the malignant tumors largely depends on the presence of facilitated glucose transporters, especially type 1 (Glut 1) and a rate-limiting glycolytic enzyme, hexokinase (HK) type II. Low expression of Glut 1 in HCCs was reported, and varying degrees of HK in HCCs which may explain the low sensitivity of FDG-PET in HCC. The poorly differentiated (high-grade) HCCs usually have higher FDG uptake, and therefore FDG-PET can predict the outcome of patients with HCC. Serum alphafetoprotein (AFP) also correlates significantly with both standardized uptake value (SUV) and tumor-to-nontumor ratio of the SUV, indicating that AFP is involved in glucose metabolism and cell proliferation in HCC. Besides, FDG-PET does have the advantage over the other modalities in its whole body imaging, which allowing the detection of extrahepatic disease. In the monitoring of patients with HCC, FDG-PET provides metabolic changes occurring after treatment earlier than structural changes (Fig 21). *(Chen et al.,2008).*

**Fig (21):** The transverse section [T1 with contrast] (A) and coronal section [T2 without contrast] (B) of MRI images demonstrate an about 2.72 cm hypervascular tumor (arrow) in the inferior posterior segment of liver. *(Chen et al.,2008).*
α-Fetoprotein level:

Measurements can be very helpful in the diagnosis of HCC. An AFP level greater than 20ng/mL is noted in about three fourths of documented cases of HCC. False-positive elevations of serum AFP can be seen in inflammatory disorders of the liver, such as chronic active viral hepatitis. Specificity and positive predictive values of AFP improve with higher cutoff levels (e.g., 400ng/mL), but at the cost of sensitivity. With the improvements in imaging technology and the ability to detect smaller tumors, AFP is largely used as an adjunctive test in patients with liver masses. In fact, a hypervascular mass consistent with HCC combined with an AFP higher than 400ng/mL is diagnostic. AFP levels are particularly useful in monitoring treated patients for recurrence after normalization of levels (Harisinghani, 2000).

Liver Biopsy:

The role of image-guided percutaneous biopsy has become less important as the sensitivity and specificity of radiologic imaging studies had improved. In patients with a clinical picture and radiologic findings that point to a specific type of lesion, percutaneous biopsy is rarely indicated to initiate liver-directed therapy. In patients in whom the diagnosis is not evident based on clinical and radiographic grounds, a percutaneous biopsy can be done safely using either ultrasound or CT guidance (Fig. 22). The target lesion should be accessed through a quantity of normal liver tissue sufficient to avoid free rupture of tumor into the peritoneum. This is especially important with HCCs, which are friable and vascular lesions (Peterson and Baron, 2001).
Fig (22): (A) Percutaneous liver biopsy. A, contrast-enhanced CT. Shows liver mass (arrow) in the right lobe of the liver.

(B) Percutaneous biopsy was performed to obtain material for cytologic and pathologic diagnosis

*(Peterson and Baron, 2001)*

**Diagnostic Laparoscopy:**

The last step in liver imaging to be considered is diagnostic laparoscopy. The goal of the preoperative evaluation of HCC is to detect surgically treatable disease. This includes identifying contraindications to resection or ablation such as extrahepatic disease, extensive intrahepatic disease, and portal hypertension. Although some controversy exists as to the utility of diagnostic laparoscopy, the ability to evaluate the entire abdomen, including the parietal and visceral peritoneal surfaces, perform intraoperative laparoscopic ultrasound, and evaluate the porta hepatis in a minimally invasive manner is compelling.
A number of patients undergoing exploration for liver malignancy will have evidence of unresectability. Patients presenting with more than three lesions are at higher risk of having occult metastases identified compared with patients with solitary lesions. A complete diagnostic laparoscopy including laparoscopic ultrasound can be performed in less than 20 minutes. Strong consideration should be given for the use of diagnostic laparoscopy as the final step in patient staging for HCC (Giger et al., 2002).

**Evaluation of Functional Hepatic Reserve:**

Patients with normal hepatic parenchyma and serum liver tests can tolerate resection of as much as 80% of their liver volume. The remaining 20% of normal, perfused liver has the metabolic capacity to provide adequate hepatic function while liver regeneration occurs. However, patients with abnormal liver function related to extensive fatty infiltration or cirrhosis, may not tolerate resection of a significant proportion of the liver and are at increased risk for postoperative liver insufficiency or liver failure and death. Assessing the risk of postoperative liver failure based on a clinical classification system, such as the Child's paugh class (Table 3) alone is inadequate; the postresection mortality rate from liver failure for Child's paugh class A or B patients ranges from 8 to 25%. (Curley, 2006).

In cirrhotic patients being considered for resection of HCC, the addition of functional hepatic studies can improve patient selection, determine the extent of hepatic parenchymal resection that will be tolerated, and reduce the postoperative mortality rate from liver failure to between 0 and 5%. Functional studies of the liver employ compounds that normally are rapidly acquired and metabolized or cleared by hepatocytes.
Rates of metabolism and clearance are decreased in cirrhotic or diseased livers. Some of the compounds used in functional studies have a clearance rate that is determined principally by the route of delivery rather than metabolism. Hence these compounds reflect changes in hepatic microcirculation and reduction in hepatic blood flow associated with cirrhosis. Other compounds are less affected by blood flow rates, and their metabolism is a more accurate indicator of functional hepatocyte mass (Kobayashi et al., 2004).

The most commonly used tests to assess functional hepatic reserve are:

**Indocyanine green (ICG) clearance test:**

ICG is an anionic dye bound by plasma lipoproteins which is rapidly cleared by the liver and excreted unconjugated in bile. Hepatic clearance is limited by both the hepatic blood flow rate and uptake by hepatocytes. Following an intravenous bolus of ICG, the kinetics of its disappearance from plasma due to hepatic clearance can be used to estimate the functional hepatic reserve in patients with cirrhosis or extensive fatty infiltration. ICG clearance determinations are widely used and readily available (Lau et al., 1997).

**Aminopyrine and phenylalanine breath tests:**

There are several tests that assess functional hepatic reserve that are not dependent upon hepatic blood flow rate. These tests can provide a more accurate measure of hepatocyte uptake and metabolism. The aminopyrine and phenylalanine breath tests are noninvasive and reasonably simple to perform.
The patient ingests an oral dose of radiolabeled $^{14}$C aminopyrine or L-$^{13}$C phenylalanine, then the individual breathes into an apparatus that collects expired CO$_2$ at intervals for up to 2 hours after the radiolabeled compound is ingested. The amount of exhaled $^{14}$CO$_2$ or $^{13}$CO$_2$ is then used to calculate the percentage of the original aminopyrine or phenylalanine dose undergoing hepatic demethylation or oxidation (Sherlock et al., 1978).

**Galactose clearance:**

Another test of hepatocyte microsomal capacity involves an intravenous injection of galactose followed by serial measurement of serum galactose levels to determine hepatic clearance of galactose. This test is not affected by altered hepatic blood flow rates that may occur with cirrhosis. Both of the radio label tracer studies and galactose eliminate rate have been shown to increase the predictive accuracy of postoperative liver failure in cirrhotic patients with borderline abnormal ICG clearance rates (Curley, 2006).

**Lidocain clearance test:**

Administering a known intravenous dose of lidocaine to determine the rate of hepatic microsomal metabolism of lidocaine to monoethylglycinexylidide (MEGX) is another method of evaluating liver function. This test is less expensive, simpler, and provides an assessment of functional hepatic reserve more rapidly than other clearance studies (Meyer-Wyss et al., 2005).
Treatment Of HCC

Hepatocellular carcinoma (HCC) has five characteristics that are strikingly different from those of other malignant tumors of the digestive system:

1. A strong causal relationship with hepatitis viruses (especially type B and type C).
2. A major impact of the status of hepatic functional reserve and liver damage on the choice of treatment and the prognosis.
3. A high recurrence rate, with many of the recurrences developing within the liver, and the existence of two major routes of recurrence, i.e., multicentric carcinogenesis and intrahepatic metastasis.
4. The possibility of performing effective treatment, if confined to the liver and liver functional reserve permits.
5. The existence of a clear outcome determinant as vascular invasion.

Because of these characteristics, choosing the method of treatment for HCC is not easy, although several useful methods are available to treat HCC.

Three methods of treatment are currently recognized as effective against HCC: surgery, including liver resection and liver transplantation, percutaneous ablation therapy as represented by radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), and transcatheter arterial chemoembolization (TACE). Because almost all cases of HCC are associated with chronic liver damage in some degree, liver function conditions must be taken into consideration at the same time as tumor
conditions when choosing treatment. Thus, treatment selection conditions are complicated. Especially, it is difficult to select surgery or percutaneous ablation therapy. Because studies that have evaluated the results of treatment scientifically have been inadequate, whenever it has been possible to select more than one method of treatment under certain tumor and liver function conditions, the choice has often ultimately depended on the skill and convictions of the attending physician, customary practice at the institution (Hasegawa and Kokudo, 2011).

The role of adjuvant or neoadjuvant therapy is being investigated, but there is no clear evidence supporting its routine use at this time. Some have proposed expanding size criteria for transplantation or downstaging tumors detected beyond an early stage, although any benefits must be weighed against the harms to others on the waiting list. For intermediate-stage HCC, transarterial chemoembolization is the mainstay of treatment but is only possible in a minority of patients. The role of radiation therapy for these patients continues to be refined with recent advances in technology minimizing its toxicity to surrounding nonmalignant liver. For patients with advanced HCC, sorafenib is the first systemic therapy to significantly prolong survival and is now considered standard of care for patients with Child A cirrhosis and good performance status (Singal and Marrero, 2010).
Treatment options

A number of treatment options, including resection, thermoablation, chemoembolization, alcohol injection and orthotopic liver transplantation, are available for patients presenting with HCC with a cirrhotic liver (Table 7) (Jonas et al., 2001).

The best treatment for each patient with HCC is dependent upon numerous factors:

- Size.
- Number of lesions.
- Tumor grade.
- Hepatic reserve.
- Patient age.
- Patient overall medical condition. (Martin and Benedict., 2005).

Therapy for HCC requires a multidisciplinary approach with input from the surgeon, hepatologist, medical oncologist and interventional radiologist (May and Mulcadhy., 2005).
Table (7): Treatment Options for Hepatocellular Carcinoma (Jonas et al., 2001).

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<td><strong>Surgical</strong></td>
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<td>• Resection with or without preoperative portal vein embolization.</td>
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<td>• Liver transplantation.</td>
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<td><strong>Image-Guided Tumor Ablation</strong></td>
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<td>• Chemical Ablation:</td>
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<td>- Percutaneous ethanol injection.</td>
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<td>- Percutaneous Acetic Acid Injection.</td>
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<td>• Thermal Ablation:</td>
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<td>- Radiofrequency Ablation.</td>
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<td>- Cryoablation.</td>
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<td>• New Nonchemical Nonthermal Ablation:</td>
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<td>- Irreversible Electroporation.</td>
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<td>- Light-Activated Drug Therapy</td>
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<td><strong>Image-Guided Transcatheter Tumor Therapy</strong></td>
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<td>• Transarterial Embolization.</td>
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<td>• Transarterial Chemoembolization.</td>
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<td>• Chemoembolization with Drug-Eluting Beads.</td>
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<td>• Transarterial Chemoinfusion.</td>
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<td><strong>Systemic targeted therapy</strong></td>
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59
surgical treatment

Surgical planning:

After assessment of the patient's fitness, the severity of underlying chronic liver disease, and the resectability of the tumor (by radiological evaluation) has been done, the patient is offered surgery if he or she has a resectable HCC (absence of portal vein invasion, size around 5cm, no extra-hepatic disease), no underlying liver disease, or well compensated cirrhosis (i.e. child's A). Liver resection is the treatment of choice in non-cirrhotic patients with HCC. For those with cirrhosis or end stage liver disease, transplantation remains the most worthwhile option, along with a most of other non-operative means of achieving tumor controls (Sujoy and Girish, 2001).

In patient with sporadic hepatoma, the liver has a normal ability to regenerate. Thus, a radical resection by removal of the lobe containing the tumor is optimal. Large size is not barrier to surgical resection providing that there is no distant spread and the tumor can be completely removed. It is certainly the case that large diameter tumors have a worse prognosis than the small ones. (Primrose, 2002).

Surgical treatment of HCC include:

1. Hepatic resection.
2. Liver transplantation.
1. Hepatic Resection

Hepatic resection has been and remains the primary treatment for HCC in patients with limited disease. Resection has several advantages over transplantation. First, it is more widely applicable because there are no restrictions on tumor size or vascular proximity—variables that often preclude transplantation and ablation, respectively. In addition, there is no obligatory waiting time before proceeding with resection, as is the case with liver transplantation, and unlike ablative therapy, resection allows complete pathologic assessment of the specimen. Of course, the efficacy of partial hepatectomy depends on the ability to achieve a complete resection (R0) that leaves behind an adequate liver remnant. Like transplantation, disease extent is closely linked with outcome after resection, with the best results achieved in patients with solitary small tumors confined to the liver. In addition, resection is largely limited to patients with normal liver or Child-Pugh class A cirrhosis, and unlike transplantation, resection does not address the diseased precancerous liver remnant (Nathan et al., 2009).

Types Of Hepatic Resection:

- Open Resection.
- Laparoscopic Resection. (Blumgart et al., 2000).
1. Open Hepatic Resection

**Types of resection:**

Resection of up to 70-80% of the liver can be performed safely, with compensatory hypertrophy and hyperplasia occurring within 3-6 weeks resulting in a regenerated liver of approximately normal size. Recently through understanding of hepatic anatomy and physiology and improved anesthetic and hematologic support contributed to the decreased perioperative mortality such that liver resections now routinely carry lower than a 5% mortality, even extensive. *(Yang et al., 2002).*

The type of liver resection performed depends in large part upon the size and location of the tumor. Hepatectomies can be classified according to either the anatomical segments described by Couinaud (1957) or Goldsmith & Woodburne (1957), or according to the surgical technique *(Jarnagin et al., 2002).*

**Classification of hepatectomies:**

**A- Anatomical classification:**

Liver resection can be separated into two groups:

1. Typical hepatectomies which are defined by the resection of a portion of liver parenchyma following one or several anatomical scissurae. These resections are called hepatectomies (Left or right), sectoriectomies, and segmentectomies.

2. Atypical hepatectomies which consist of the resection of a portion of parenchyma not limited by anatomical scissurae.
The most common typical hepatectomies can be separated into two groups. Firstly, there are right and left hepatectomies in which the line of transection is the main portal scissura separating the right and left livers. Secondly, there are right and left lobectomies in which the line of transection is the umbilical fissure. In the classification of Couinaud, right lobectomy corresponds to a right hepatectomy extended to segment IV. The terms left or right lobectomy are frequently used in the Anglo-Saxon literature to define what is, in fact, a left or right hepatectomy. It is preferable, to avoid referring to as lobectomy the resection of a part of the liver that does not fit with the anatomical definition of the lobe. In order to avoid confusion some have recently proposed the omission of the words( right lobectomy) for any kind of right liver resection and to use the word right hepatectomy extended to the segment IV or right hepatectomy extended to the segment IV and I when the segment I is also removed. On the left, for the resection of the classical left lobe (Segment II and III), it seems difficult to avoid speaking of left lobectomy; left lateral segmentectomy is anatomically wrong for the true left lateral segment (or sector) is only segment II. (Fig. 23,24,25 ) illustrates the differences in definition of hepatectomies. (Blumgart et al., 2000).

B- Technical classification:

-Hepatectomy with preliminary vascular ligation.
-Hepatectomy by primary parenchymal transection.
-Hepatectomy by selective clamping.
-Hepatectomy under total vascular occlusion.
-Hepatectomy with intermittent pedicle clamping.
-Hepatectomy by suprahilar clamping. (Sujoy and Girish, 2001).
Fig. (23): Superextended hepatectomies include resection of at least six segments on the right and at least five on the left. Extended hepatectomies include five on the right and four on the left. (Bismuth and Vibert, 2007).
Fig. (24): Major hepatectomies include resection of four segments on the right and three segments on the left. Note that the term trisegmentectomy refers to three Couinaud segments. (Bismuth and Vibert, 2007).
Fig. (25): Limited hepatectomies include resection of two segments, such as a left lobectomy (segments 2 and 3) and bisegmentectomy (e.g., segments 6 and 7 or 5 and 8) (central bisegmentectomy). *(Bismuth and Vibert, 2007).*
1. **Laparoscopic Hepatic Resection**

There are three different terminologies that have been used with regard to laparoscopic liver resections:

1. Pure laparoscopic.
2. Hand-assisted laparoscopic resection.
3. Laparoscopic-assisted (hybrid) open resection.

There is no clear advantage of one approach over the others. All aim to reduce the surgical trauma by minimizing the length of surgical incision. An incision is often required to extract the tumor specimen and one may as well make this incision at the beginning if it will aid the dissection. *Poon* has reported the following advantages with the insertion of a hand port:

1. Palpation with the hand and the use of intraoperative ultrasonography through the hand port improve the staging of tumor and permit better delineation of resection margin.
2. The hand is the best retractor.
4. Hand assistance in intracorporeal suturing.
5. Specimen retrieval through the hand port. (*Poon*, 2007).
**Indications:**

**Tumor Location**

HCC located in antero-lateral segments of the liver (segments 2–6, so called laparoscopic segments) and scheduled for wedges, segmentectomies, and left lateral sectionectomies are the best indications for laparoscopic approach. Laparoscopic right hepatectomy can be planned for HCC located anywhere in the right lobe with the exception of those close to the hilum or the hepato-caval junction, because of the risk of major vascular or biliary injury. The role of laparoscopy for lesions requiring resections of segments 7, 8, and 1 is not yet codified. Even if they have been traditionally considered non-laparoscopic segments because of difficult visualization of surgical field, hand-assisted laparoscopy and thoracoscopy have been proposed in such location. *(Bryant et al., 2009).*

*Cho et al.* recently reported a series of 36 patients with lesions located in postero-superior segments (Sg7-8-4a-1) treated by pure laparoscopic approach (Figs.26-27-28-29).
Fig (26): The “laparoscopic segments.” Shaded areas are considered consistent with laparoscopic resection. *(Bryant et al., 2009).*

Fig (27): Laparoscopic left lateral sectionectomy for HCC. (a) Preoperative CT scan. (b) The surgical field at the end of parenchymal transection. (c) The specimen. *(Cho et al., 2008).*
Fig (28): Laparoscopic atypical resection of segment 8 for HCC. (a) Preoperative MRI. (b) Liver transection performed with harmonic scalpel. (c) Specimen is placed in a plastic bag. (d) Specimen extraction through a separate incision. (e) The surgical field at the end of parenchymal transection. (f) The specimen. (Cho et al., 2008).
Fig (29): Laparoscopic segmentectomy 4b for HCC. (a) Preoperative CT scan. (b) The surgical field at the end of parenchymal transection. (Cho et al., 2008).

**Tumor Size**

laparoscopy is usually not recommended for HCC exceeding 5 cm of diameter. (Sasaki et al., 2009).

**Liver Function**

Liver function is an essential component of selection of patients considered for liver resection for HCC. In open surgery only Child–Pugh A patients with a future remnant liver over 40% are considered for liver resection. The same criteria should be adopted for laparoscopic liver resection. In case of peripheral nodules requiring atypical resections, some authors proposed laparoscopic liver resection in patients with poor liver function (Child–Pugh B) (Fig.30). (Torzilli et al., 2008).
Fig (30): Laparoscopic atypical resection of segment 2 as a “bridge” to liver transplantation for HCC in Child–Pugh B patient. (a) Preoperative MRI. (b) The specimen. (c) Postoperative CT scan, 1 month after the laparoscopic resection. (Torzilli et al., 2008).

- **Surgical Technique:**
  
  The use of two monitors is recommended. Although some groups use 0° laparoscopes. 30° laparoscopes are preferred by most authors. (Dagher et al., 2007).

**Patient Positioning**

There is two different positions according to lesion site. For lesions located in segments 2 through 5 (the majority of cases), the patient is placed in the supine position, with lower limbs apart (Fig.31).
The surgeon stands between the legs with one assistant on each side. For patients with lesions of segment 6 scheduled for atypical resection or segmentectomy, the left lateral decubitus position may be used in order to expose the lateral and posterior aspect of the right liver (Fig.32) In this case the surgeon is on the ventral side of the patient. In case of laparoscopic right hepatectomy, supine position with lower limbs apart is preferred. *(Koffron et al.,2007).*

**Fig (31):** Port placement for resection of lesions located in segments 2–5 and for right hepatectomy. The patient is in supine position with lower limbs apart and the surgeon between the legs. Numbers shown represent trocar sizes in millimeters. *(Koffron et al.,2007).*
Fig (32): Port placement for resection of lesions located in segment 6. The patient is in left lateral decubitus for right lobe mobilization and posterior exposure. The table can be turned to the right to reapply the right lobe and gain anterior access. Numbers shown represent trocar sizes in millimeters. (Koffron et al., 2007).

Port Sites Positioning and Hand Assistance

Positioning of port sites is different according to tumor site and it is shown in Figs. (31) and (32). Many variants have been described. The position of trocar for the laparoscope can be higher on the midline or more lateral on the right side in case of right liver resection. (Dagher et al., 2007).

Hand-assisted laparoscopy is used by several authors. It consists in the placement through an 8-cm incision of a gas-tight port permitting the introduction of a hand in the abdomen. The assisting hand allows tactile feedback while palpating the liver and it may help in abdominal exploration, mobilizing the liver, provides gentle retraction, and helps during parenchymal transection. In addition, in case of bleeding hand compression allows easier hemostasis. For its proponents, this technique may render laparoscopic liver resection safer and more accessible.
Hand assistance has been used in selected cases (about 10%) of right hepatectomies or limited resections of posterior right segments to facilitate when liver mobilization or parenchymal transection can be difficult. *(Huang et al., 2009)*.

**Pedicle Clamping**

Intermittent clamping (15-min clamping and 5-min release periods) can be performed whenever necessary. Our group demonstrated that in patients with normal cardiac function laparoscopic pedicle clamping is safe and well tolerated. However, it is used less often and the majority of recent resections have been performed without any clamping even in cirrhotic patients. *(Viganò et al., 2009)*.

**Liver Mobilization and Inflow/Outflow Control**

In left lateral sectionectomy, the round, falciform, and left triangular ligaments and the lesser omentum are divided. Dissection of the falciform ligament is continued to the level of the inferior vena cava and the insertions of the hepatic veins. Parenchymal transection is carried out until the portal pedicles of segments 2 and 3 are exposed. The pedicles are then divided using linear staplers. Left hepatic vein is divided at the end of parenchymal transection by linear stapler.

In limited resections, parenchymal transection is carried out along decided transection lines. Portal pedicles and hepatic veins are controlled as they are encountered during transection. In limited right-sided resections, the right triangular ligament is divided, taking advantage of the lateral position of the patient. Parenchymal transection is then carried out.
Laparoscopic right hepatectomy includes dorsal decubitus position, initial division of the right portal pedicle, right liver mobilization, taping of right hepatic vein if feasible and transection. Hand assistance can be used. Hand port is introduced through a right iliac or flank transverse incision. Surgeon’s left hand or assistant’s right hand helps mobilizing the liver and compresses in case of bleeding. *(Chang et al., 2007).*

**Parenchymal Transection**

The main technical challenge of laparoscopic liver resection remains hemorrhage during parenchymal transection, especially in cirrhotic patients. Several devices have been developed with the aim to perform more bloodless and accurate parenchymal transection. These devices have not proved to be indispensable during open resections. However, in laparoscopic surgery, the simple principles of transection are more difficult to apply and some of the newly designed technologies are required.

**The Ultrasonic Aspirator** – The ultrasonic dissector selectively destroys liver parenchyma and spares vessels and bile ducts that can be selectively controlled. It does not have hemostatic properties. It is particularly useful in deep parenchymal transection, especially in right hepatectomy, to selectively identify and control vessels and bile ducts.

**The Ultrasonic Scalpel** – Also called harmonic scalpel, it has the major advantage to cut and coagulate at the same time. In the laparoscopic procedures, easy handling and rapid action are major advantages of this device. It can be particularly recommended for the
superficial parts of transection (2 cm in depth). However, it is a blind instrument which should be used with caution when deeper liver parts are reached because of the risk of vascular injuries to larger vessels, especially to hepatic veins.

**The Vessel Sealing System** – The vessel sealing system uses low-frequency bipolar current and seals vessels up to 7 mm in diameter. Its use is rather similar to that of the ultrasonic scalpel, and it includes a knife that cuts after sealing.

**Radiofrequency-Assisted Hepatic Resection** – The radiofrequency probe inserted along transection line generates pre-coagulation. Subsequent cut along coagulated line can be performed. Many advantages have been suggested: easy and bloodless transection, mainly in atypical resections; it can be helpful in wedge resections, in which visualization of transection planes and bleeding control may be more difficult; induced necrosis may improve safe surgical margins. Further studies are needed to evaluate its role in laparoscopic liver surgery.

**Stapler Hepatectomy** – Linear stapler devices are widely applied in laparoscopic liver surgery for portal pedicles and hepatic veins division. Recently, some authors proposed their use for parenchymal transection. After the transection line is marked and the liver capsule is incised with diathermy, liver parenchyma can be divided with repeated applications of linear vascular staplers. According to its proponents, this technique allows fast and safe resection. However, vascular and biliary injuries can occur during blind transection and this technique does not allow fine control of margins and requires that tumors are located remotely from the transection line.
In addition, the cost of this method is high and increases with the number of applications required. *(Viganò And Cherqui.,2011).*

- **Complications of laparoscopic liver resection :**
  1- Bleeding which is more difficult to control during laparoscopy than open approach.
  2- The laparoscopic approach carries an increased risk of gas embolism compared with open approach.
  3- The procedure may convert to an open approach because of presumed invasion of the surgical margin during the resection.
  4- Tumor exfoliation and port- site metastases.
  5- Trocar site hernia. *(Hashizume et al.,2000).*
2. Liver Transplantation

Patient selection:

HCC is usually a slow-growing malignancy. However, the fact that it appears in the cirrhotic patient as well as its tendency to multifocality and to recurrence after therapy recommend liver transplantation as a logical way to deal with both malignancy and liver disease. (Martin, 2007).

In the early 80’s, as soon as liver transplantation became an accepted standard therapy for end-stage liver disease, the indication for liver replacement was extended, somehow indiscriminate, to patients with liver tumors. After initial poor results, the transplant community learned that recurrence and progression of malignancy are very rapid under immunosuppression and that the indication for transplantation should be limited to carefully selected patients. Number and size (>5 cm) of tumors, and vascular invasion were identified as poor prognostic factors and patients with extrahepatic disease were excluded from transplantation. (Yokoyama et al., 1990).

In time, other factors that affect survival and recurrence were identified, such as positive nodes and histologic grading. (Klintmalm, 1998). An accurate preoperative staging seems to have a beneficial effect on tumor recidive. (Shah et al., 2006).
In 1996, Mazzaferro et al. published a landmark study, imposing the so-called “Milan Criteria”. This study showed that patients with up to 3 tumors, none larger than 3 cm, or 1 tumor < 5 cm had an excellent survival, while patients exceeding these criteria had a significantly worse outcome.

Even though data from the University of California at San Francisco (UCSF) and from the Mount Sinai Medical Center in New York showed that acceptable survival and disease-free survival rates can be achieved in patients with slightly higher tumor load, there is still not enough information to impose the routine transplantation of patients with higher tumor burden (Table 8). (Yao et al., 2001).

Multimodal approaches with preoperative downstaging via TACE and postoperative chemotherapy seem to benefit certain patients with tumor extension beyond Milan criteria. (Roayaie et al., 2004).

Table (8): The "Milan Criteria" defined by Mazzaferro in 1996 define the tumor load within which the survival rates are similar to those of patients without malignant disease. Some institutions like the University of California at San Francisco (UCSF) try to extend the indications to limits where the survival and recidive rates are still acceptable.

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**Milan Criteria (Mazzaferro et al, 1996)**
- Single tumor ≤ 5 cm, or
- 2–3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread

**UCSF Criteria (Yao et al, 2001)**
- Single tumor ≤ 6.5 cm, or
- 2–3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm
- No vascular invasion and/or extrahepatic spread
Liver transplantation for patients with hepatocellular carcinoma is of theoretic advantage because it should overcome the following problems:

1. Lesions that are unresectable because of size or multifocal distribution.
2. The inability of a cirrhotic liver to tolerate liver resection.
3. The likelihood in many cases that an undetectable second tumor is located remote from the index lesion.

The results of liver transplantation have been good for fibrolamellar carcinoma 5-years survival rates is about 50%. In patients with clinically apparent HCC complicating cirrhosis, 5 years survival is about 35% good enough to encourage further efforts. The results are almost twice as good for patients with just one locus of tumor. Therefore, although the logistical problems and expense are enormous, transplantation is presently the best treatment for HCC in a cirrhotic liver (Gerard & Lawrence, 2003).

In 1963, Strazl and his group carried out the first successful hepatic transplantation in man. The number of liver transplantation is increasing, improved results can be related to more careful patient selection to better surgical techniques and post-operative care, better immunosuppressant and to great willingness to re-transplant after rejection (Neuberger & James, 1999).
Currently 1-year survival rates range from 54% to 83%. The dramatic increase in the survival rates results from the following factors:

1. Advances in standardization of the transplantations.
2. Expertise of anesthesiologists in the prevention and treatment of the metabolic abnormalities that occur in patients with end-stage liver disease during the transplantation procedure.
3. Use of the venovenous bypass system, which ensures venous return to the heart from both portal and systemic venous system during the an-hepatic phase of the transplantation procedure, reduces blood loss, decreases the incidence of postoperative renal failure and generally results in less hemodynamic instability during the procedure.
4. Improved techniques for the identification and support of potential organ donors.
5. Refinement of operative techniques for the recovery and preservation of the donor livers.
6. Use of more effective and less toxic immunosuppressive regimens (Gupta, 1999).

**Indications for liver transplantation in HCC:**

1. Unavailability of other surgical or medial therapies that offer the patient an opportunity for long-term survival.
2. The tumor must be 5cm. or less. If multifocal, only three tumors less than 3cm. each should be considered. Transplantation may be preferable to resection for small tumors discovered incidentally in a patient with compensated cirrhosis.
3. Fibro-lamellar carcinoma: the tumor should be localized to the liver and in absence of cirrhosis. This may be the best tumor candidate for transplantation.

4. Absence of complications of chronic liver disease. That may significantly increase the patient's operative risk (Sugawara et al., 2003).

Contraindications:

Absolute:

1. Psychological, physical, and social inability to tolerate the procedure.
2. Active sepsis.
3. AIDS.
4. Metastatic HCC.
5. Advanced cardiopulmonary disease.

Relative:

1. Age more than 60
2. Prior porta-caval shunt.
3. Prior complex hepato-biliary surgery.
5. Re-transplantation.
7. Obesity.
8. Serum creatinine more than 2mg/dl.
9. Advanced liver disease.
Pre-transplantation evaluation of liver transplant recipients:

**A. Goals**: Once the attending physician identifies a patient as a potential candidate for liver transplantation, the patient is referred to a transplant center where the patient undergoes a thorough evaluation to satisfy four specific goals:

1. Establishment of the diagnosis.
2. Documentation of the severity of the disease.
3. Identification of all complications of the disease or concomitant diseases that might adversely affect the patient's survival.
4. Estimation of the long term prognosis of the disease with or without liver transplantation (*Tillman, 2001*).

**B. Testing**: The routine evaluation process involves a number of laboratory tests and X-ray studies:

- ABO blood grouping.
- Prothrombin time.
- Serum electrolytes.
- Blood glucose.
- Complete blood cell count.
- Partial thromboplastin time.
- Total protein and albumin.
- Total and direct bilirubin.
- Aspartate aminotransferase and alanine aminotransferease.
- Alkaline phosphatase.
- Serum cholesterol.
- Alfa feto protein, CA 19-9 and CA 50.
- Viral serologies (human immunodeficiency virus, hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus.

- Infection serologies (Rapid plasma reagin, toxoplasmosis and rubella).

- Urine analysis and culture.

- Chest X-ray.

- Electrocardiogram and cardiac catheterization.

- Arterial blood gases.

- Dobutamine stress echocardiography.

- CT or MR scan of the abdomen.

- Pulmonary function tests.

- Esophagogastroduodenoscopy.

- Doppler ultrasonography of the portal venous system to measure portal vein flow and to confirm its patency.

- Bone scan (*Tillman, 2001*).

Once accepted as an active candidate for liver transplantation, the patient is placed on the active transplantation list. When a potential liver donor is identified and located, all suitable candidates on the active list are reviewed by the transplantation committee and priority is given to the patient with the most urgent need. The chosen recipient is admitted to the transplant hospital on an emergency basis and is surgically prepared to receive the donor organ (*Lucey, 1997*).
Donor selection:

Donor evaluation is performed using an evaluation process we have previously reported. The leading causes for donor declination are significant medical history, ABO blood group incompatibility, and psychosocial history.

Living donor liver transplantation (LDLT) has developed on the basis of increased safety of conventional liver surgery and the need for expanding donor sources, especially in children. Indications for LDLT were soon extended to adult patients in Japan, where cadaveric donation was limited. Assessing the suitable size or quality of the graft, as well as of the remnant donor liver, is one of the most important problems in adult LDLT. Further investigation is needed to improve the outcome of liver transplantation across the ABO blood group barrier (Shimazu and Kitajima, 2004).

Contraindications to donation are:

1. HIV-positive status.
2. Evidence of systemic infection or malignancy.
3. Massive or irreversible hepatic injury.

The technique of preserving the liver grafts after removal from the donor is based on decreasing metabolic requirements by keeping the graft cold. Blood is flushed from the organ to prevent vascular occlusion; preservation solution is infused; the organ is kept on ice. The University of Wisconsin (UW) preservation solution contains high-molecular-weight sugar molecules that do not diffuse into the cell, which keeps the cells from swelling. These sugars and glutamine act as free oxygen radical
scavengers, which are thought to prevent injury upon reperfusion of the graft. The UW solution has extended the period of safe in vitro liver preservation from two hours to more than 36 hours (Fung et al., 2006).

The donor operation:

The hepatic structures are dissected and the liver is pre-cooled through the portal vein with Ringer's lactate and 1000ml of University of Wisconsin (UW) solution perfused through the aorta and portal vein. After removal, the cold liver is further flushed with an additional 1000ml UW solution through the hepatic artery and portal vein and stored in this solution in a plastic bag on ice in a portable cooler. The size of the donor liver should be matched to that of the recipient occasionally a small-sized liver is transplanted into a larger patient. The donor liver increases in size until it achieves the volume expected for the recipient's size, age, and sex (Gerard & Lawrence, 2003).

The recipient operation:

Whole-organ liver transplantation, the average operative time is 8 hours. Blood loss is variable, volumes being minimal or massive. The blood is aspirated from the abdominal cavity, washed repeatedly, re-suspended and infused.
Transplantation of the liver comprising three distinct sequential phases:

The first phase:

The abdominal wall incision used by most surgeons is a bilateral subcostal incision that is extended in the upper midline. The xiphoid process is excised. The diseased liver, the hilar structures and vena cava above and below the liver are dissected.

The second phase:

Known as the (anhepatic phase), refers to the period starting with devascularization of the recipient's liver and ending with revascularization of the newly implanted liver. The various vessels are cross-clamped and divided to allow removal of the liver. During the anhepatic phase, veno-venous bypass (VVB) may be used to prevent pooling in the lower part of the body and splanchnic congestion (Fig.33). The cannulae are placed in inferior vena cava (via the femoral vein) and the portal vein, and run to the subclavian, axillary, or jugular veins. Maintenance of venous return from the kidneys and lower extremities during the anhepatic phase results in a smoother hemodynamic course, allows time for a more deliberate approach to hemostasis, reduces visceral edema and splanchnic venous pooling and lower the incidence of postoperative renal dysfunction (Fan et al., 2002).
Fig. (33): Venovenous bypass system in place during the anhepatic phase of transplantation procedure (Griffith, 1995).

The liver allograft is implanted by anastomosing first the supra-hepatic vena cava and then the infra-hepatic IVC. The portal vein anastomosis is performed and blood flow to the liver is reestablished. The patient is taken off VVB and the hepatic arterial anastomosis is performed (Fig. 34) (Ghobrial, 1999).
Fig.(34): Supra-hepatic vena caval anastomosis during implantation of the donor liver (Henderson and Rikkers, 1996).

The third phase:

Includes biliary reconstruction and abdominal closure. Biliary continuity via a duct-to-duct anastomosis over a T tube. (Fig.35) (Ghobrial, 1999).
Fig.(35): Complete hepatic trasplantation procedure, showing the liver in the normal orthotopic position and all anastomoses completed (Starzl and DeMetris 1990).

**Role of orthotopic liver transplantation:**

Most hepatologists consider orthotopic liver transplantation (OLT) as the treatment of choice in cirrhotic patients with early HCC. Recent studies have indicated that OLT should be restricted to patients with single tumors of less than 5cm or with three nodules, each less than 3cm in the absence of any portal vein thrombus or extra-hepatic spread (Molmenti and Klintmalm, 2002).
The resultant 5-year survivals range between 60% and 70% and these are much better than the survival rates available for liver resection alone in a similar group of patients. In fact, the best results were obtained when OLT was done for occult/incidental HCC that were not identified during pre-transplant evaluation, survival at one year; 90% and at 5 years, 70%; recurrence rate, 13%) (Bismuth et al., 1999).

Liver transplant is the only treatment that offers complete removal of the tumor and the underlying chronic liver disease simultaneously, thereby eliminating a fertile soil for recurrence and obviating Post-resectional liver failure. Most centers feel that recurrence after OLT can be minimized by applying stringent selection criteria. The Pittsburgh group have evolved a Prognostic Risk Score (PRS) based on their data for 344 patients who underwent liver transplantation in the presence of HCC Table (9). (Iwatsuki et al., 1999).

Table (9): Prognostic Risk Score Grading for Tumor Recurrence. (Iwatsuki et al., 1999).

```
Grade 1 0 ≤ Risk score < 7.5
Grade 2 7.5 ≤ Risk score ≤11.0
Grade 3 11.0 < Risk score <15.0
Grade 4 Risk score ≥ 15.0
Grade 5 Positive margin, lymph node, or metastasis
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Multivariate analysis revealed three factors to be associated with poor prognosis:

1. Bilobed tumors.
2. Size of the largest tumor more than 5 cm.
3. Vascular invasion (microscopic and macroscopic).

The prognostic risk score for each patient was calculated from the relative risks on multivariate analysis, and five grades were classified. In their study, they found that the PRS system correlated extremely well with tumor-free survival after transplantation (100%, 61%, 40%, 5% and 0% for grades 1 to 5, respectively, at 5 years). They finally concluded that patients with grade 1 and 2 were most effectively treated by transplantation, and that grade 1 patients did not benefit from adjuvant chemotherapy (Sujoy and Girish, 2001).

Despite these results, the growing shortage of donor organs, and the increasing waiting times, are detracting workers from the universal utilization of OLT as a therapeutic option. In ideal scenario, in cirrhotic patients with early HCC, liver resection has a role restricted to the treatment of those patients in whom OLT is otherwise contraindicated (old age, hepatitis B infection with chronic active hepatitis), or as a first-line treatment in patients with easily accessible tumors and child's A status for whom a long wait (> 6 months) for graft is predictable and for whom a "salvage transplant at a later date may remain a viable option" (Majno et al., 2000).
Liver transplantation in noncirrhotic patients with HCC:

In regard to OLT in noncirrhotic patients with HCC, a recent review identified 126 patients reported over the past 32 years. The 5-year survival rate was greater in patients who underwent transplantation for fibrolamellar HCC (FLHCC) than for non-FLHCC (40% VS 11%) respectively. Most patients had advanced local disease not amenable to resection and data available test the importance of conventional prognostic factors were limited. HCC in non-cirrhotic patients should remain an uncommon indication for OLT. Because the long-term outcome for non-FLHCC is poor, these patients should not be offered OLT for unresectable tumors. Overall, an aggressive policy of resection is justified for all types of HCC in non-cirrhotic patients, with OLT reserved for truly unresectable FLHCC confined to the liver (Kimberly and Dilip, 2003).

Segmental (Split) liver transplantation:

The procedure have been developed to support the needs of pediatric patients awaiting appropriately sized transplants and have been used in some adults as well. The liver has a remarkable capacity for regeneration. It can be divided based on the anatomic segments of couinaud into a left lateral segment (Segments II and III) a left lobe graft (segments II, III and IV) or a right lobe graft (Segments V, VI, VII and VIII). The left lateral segment is most used in children. Comparison of the size of the donor and the recipient is used to determine the appropriate-size graft. In split liver transplants, one liver is divided between two recipients (Busuttil & Goss, 1999).
Living-donor liver transplantation:

This procedure has been developed as a result of the success of reduced liver transplantation. The left lateral segment or left lobe of the liver is usually used as the donor graft. Advantages of this procedure include reduced ischemic time and the elective nature of the operation. Adult to adult living-donor liver transplantation necessitates the use of larger right hepatic lobe. Approximately 0.1% of liver volume per patient weight (700 g for a 70-kg recipient) is required (Wachs et al., 1998).

Postoperative Care of liver transplantation:

A. Hemodynamic:

Intravascular volume resuscitation usually is required in the immediate postoperative period to overcome third-space losses. Increasing body temperature and vasodilatation. Adequate perfusion is assessed by cardiac output, urine output, and the absence of metabolic acidosis (Singe et al., 1999).

B. Pulmonary:

Ventilatory support is required postoperatively until the patient is awake, alert and is able to maintain adequate oxygenation and ventilation and demonstrates adequate hepatic function (Singe et al., 1999).

C. Hepatic graft function:

Monitoring of hepatic graft begins intra-operatively after revascularization. Signs of satisfactory graft function include hemodynamic stability and normalization of acid-base status, body temperature, coagulation studies, maintenance of glucose metabolism and bile production. Reassessment of hepatic allograft function continues postoperatively, initially every 6 hours satisfactory hepatic graft function.
is indicated by an improving coagulation profile, decreasing transaminase levels, normal blood glucose, hemodynamic stability, adequate urine output, bile production and clearance of anesthesia (*Russo et al., 2001*).

**D. Immunosuppression:**

The primary immunosuppressive agents currently used are FK 506 cyclosporine and corticosteroids.

1. **Corticosteroids:**

   Adults receive 1000mg of methylprednisolone intravenously after revascularization of the donor liver. The dosage of methylprednisolone is started by 200 mg/day and is tapered over the first 6 days by 40mg/day decrements from 200 mg/day until a baseline of 20mg/day is reached. By day 6 most patients are able to tolerate oral medications and prednisolone 20mg/day is begun. Most adult patients are discharged with this dosage of prednisolone; depending on the frequency and severity of rejection episodes, the dosage is reduced in 2.5mg decrements in the first year until a baseline of 5 to 10 mg. is reached in adult patients (*Tillman, 2001*).

2. **Cyclosporin:**

   Cyclosporin is given as a single dose (2mg/ kg. IV) before the start of the transplantation procedure, ( on the day of surgery ) and the next dose is given immediately postoperatively when the patient is in the Intensive Care Unit (ICU). If urinary output is adequate a dose of 2mg/kg is administered every 8h. All additional adjustments in dosage are based on daily cyclosporine blood levels. A cyclosporin level of 1000ng/dl by Radioimmunoassay (RIA) is accepted as ideal.
After a stable course of several months, the dosage of cyclosporine may be reduced gradually to obtain a blood level of 500 to 800ng/dl by one year after transplantation.

In patients in whom cyclosporine is not well tolerated, it may be necessary to add azathioprin 1.5 to 2.5mg/kg daily to ensure adequate immunosuppression. The most common side effects directly related to cyclosporine are hypertension, nephrotoxicity, hirsutims, gum hyperplasia, and fine motor Tremor (Denton et al., 1999).

3. Tacrolimus:

Tacrolimus is more powerful than cyclosporin in inhibiting interleukin2 (IL2) synthesis and controlling rejection. It has been used to salvage patients with repeated liver rejection. It is comparable to cyclosporin in terms of patients and graft survival, there are more adverse effects necessitating discontinuation. These include nephrotoxicity, diabetes, diarrhea, nausea, and vomiting, neurological complications (tremors and headache) are more common with tacrolimus than cyclosporin (Wiesner et al., 1998).

Adjuvant therapy in patients receiving OLT for advanced HCC:

Because the results of OLT alone for advanced HCC continue to be dismal, there is scope for the evaluation of adjuvant therapy. Recurrences occur rapidly after OLT because of undetected preoperative micro-metastases, intra-operative dissemination by surgical manipulation and acceleration of tumor growth by post-transplant immunosuppression. During the waiting period for transplantation, it is prudent to limit tumor progression by systemic chemotherapy or arterial chemoembolization.
Although published results indicate that chemoembolization causes tumor necrosis in most instances, its impact on post-transplant HCC recurrence and survival is, as yet, undefined.

Systemic chemotherapy is considered essential postoperatively and should be started as soon as possible (i.e. within the first postoperative week). Most authors employing postoperative chemotherapy protocols (usually doxorubicin, cis-platinum, mitomycin C and 5-fluorouracil) have reported improved survival over that of historical controls, with 3-year survivals of 50%-60% and 5-year survival of 50%. Chemotherapy was well tolerated, although leukopenia tended to be severe, and occasionally required the use of granulocyte colony-stimulating factor. Although the weight of evidence suggests that perioperative adjuvant chemotherapy does seem to prolong survival after OLT in patients with advanced HCC, further larger multicenter prospective and randomized studies are needed before a uniform recommendation can be made (Sujoy and Girish, 2001).

Post-transplantation complications:

A- Technical complications:

1. Complications of incisions:

Infection, hernias, and granulomas of the fascial sutures, lymphoceles are a frequent complication in these sites. Lymphoceles may require repeated aspirations or the placement of drains to allow complete resolution (Fan et al., 2002).

2. Complications related to the anastomosis of the vessels:

Usually present in the early postoperative period but may occur as late as several months to years after transplantation. These complications
include bleeding, thrombosis, stenosis, infection and pseudoaneurysm formation. Postoperative anastomotic bleeding requires re-operation in the immediate postoperative period and has been associated with a higher early mortality (Fan et al., 2002).

3. Complications related to the biliary reconstruction:

The biliary reconstruction is a frequent cause of early and late postoperative complications. Complications related to either type of biliary reconstruction are leak, stricture, infection, and formation of gallstones. T-tube removal may result in either bile peritonitis or a localized bile collection. A localized bile collection is usually amenable to percutaneous drainage, but bile peritonitis requires operative repair of the leaking common bile duct (Tung & Kimmey, 1999).

4. Subcapsular hepatic necrosis:

CT examinations of cases of subcapsular hepatic necrosis showed a nonenhancing hypodense subcapsular areas with irregular contours in the liver. Major vessels were free of obstruction. Size disproportion between the graft and the recipient abdominal cavity reduced hepatic blood flow and caused abnormal pressure points. That could result in ischemia in subcapsular areas and explain the subcapsular necrosis. Although it has good prognosis without treatment, subcapsular hepatic necrosis is important to recognize to avoid confusion with liver necrosis after vascular thrombosis (Abecassis et al., 1991).

B- Perioperative graft failure:

There are four general reasons for graft failure:

1. A technically imperfect operation.
2. Unrecognized liver disease in the donor liver.

3. An ischemic injury to the donor liver, which may occur during the death of the donor. The procurement operation, or the period of refrigeration.

4. Accelerated rejection. Host immune factors and hyper-acute rejection may result in primary failure of the liver graft (Mazariegos et al., 1999).

C. Pulmonary complications:

1. Pulmonary embolism:

   Platelet aggregates in small lung vessels. Intravascular catheters and cell debris from the liver may contribute.

2. Pneumonia:

   It is usually due to methicillin resistant staphylococcus aureus, pseudomonas and aspergillosis in the first 30 days. After 4 weeks pneumonia due to Cytomegalovirus(CMV) and pneumocystis is seen.

3. Pleural effusion:

   It is virtually constant and in about 18% aspirations is necessary (Singe et al., 1999).

D. Renal Failure:

   Oliguria is virtually constant post-transplantation, but in some renal failure is more serious. The causes include pre-existing kidney disease, hypotension and shock, sepsis, nephrotoxic antibiotics, and
cyclosporin or tacrolimus, Renal failure often accompanies severe graft rejection or overwhelming infection (*Mazariegos et al., 1999*).

**E- Rejection:**

Episodes of rejection of varying severity are virtually constant (*Denton et al., 1999*).

1. **Hyperacute rejection (antibody – mediated rejection)**

   It is rare and is due to presensitization to donor antigens. Hepatic graft loss resulting from lymphocytotoxic antibodies is difficult to document, but most observers believe that it does occur, albeit in a much less predictable fashion than with renal transplantation (*Haub et al., 1987*).

   Hyper-acute rejection manifests as deterioration of allograft function, usually in the first 3 weeks postoperatively.

   Biopsy reveals infiltration by neutrophils, endothelial cell hypertrophy, and focal deposits of fibrin. Immunofluorescence studies may show antibody and complement in the vessel wall (*Gordon et al., 1986*).

2. **Acute rejection (cell – mediated rejection)**

   Acute rejection is fully reversible, but chronic is not. The two may merge into one another, 64% of patients will have at least one episode of acute rejection, usually 5-20 days post transplantation and within the first 6 weeks. The patient feels ill, there is mild pyrexia and tachycardia. The liver is enlarged and tender. Serum bilirubin, transaminases, and prothrombin time increase (*Wiesner et al., 1998*).
Liver biopsy is essential. Rejection is shown by bile duct damage, and subendothelial inflammation of portal and terminal hepatic veins. Rejection may be graded into mild moderate and severe. Acute rejection occurs frequently but is effectively blunted by anti-rejection therapy. In modern practice, cell mediated rejection is a less common cause of graft loss than are primary non-function or hepatic artery thrombosis, still the effectiveness of anti-rejection treatment assumes a relatively early diagnosis, which is in turn the result of careful monitoring by the transplantation physician (Wiesner et al., 1998).

In 85% treatment is successful by increasing immunosuppression. Boluses of high dose methylprednisolone are given, for example 1g intravenously daily for 3 days, those who are steroid-resistant receive interlukin2 (IL2) monoclonal antibody for 10-14 days. Tacrolimus may also be tried. Those failing to respond to these measures proceed to chronic rejection. Re-transplantation may be needed if the rejection continues (Wiesner et al., 1998).

3. **Chronic rejection:**

Bile ducts are progressively damaged and ultimately disappear. Chronic rejection defined as loss of interlobular and septal bile ducts in 50% of portal tracts. Chronic rejection may be graded histologically into mild, moderate and severe. Bile duct epithelium is penetrated by mononuclear cells resulting in focal necrosis and rupture of the epithelium. Larger arteries show subintimal foam cells, intimal sclerosis and hyperplasia. Cholestasis develop and eventually biliary cirrhosis.
Chronic rejection usually follows acute rejection with bile duct degeneration. (*DeMitri et al., 1995*).

Chronic rejection is characterized by relentless immune attack on small bile ducts. Clinically, the pattern is one of gradual biliary obstruction, with elevation of alkaline phosphatase and bilirubin, in the absence of abnormalities in large bile ducts. Histologically, small bile ducts are obliterated or completely absent, with less cellular infiltrate than is seen with acute rejection (*Ludwige et al., 1987*).

**F- Infections:**

Over 50% will experience an infection in the post-transplantation period. This may be primary, reactivation, or related to opportunistic organisms. (*Wade et al., 1995*).

1. **Bacterial infections.**

These are usually seen during the first 2 months and are usually related to technical complications. They include pneumonia, wound sepsis. Deaths in transplant patients are almost always due to sepsis. (*Wade et al., 1995*).

2. **Viral infections.**

This infections is a virtually caused by Cytomegalovirus (CMV), Herpiv simplex virus and Epstein-Bar virus (*Falagas et al., 1998*).

3. **Fungal infection.**

Aspergillosis has a high mortality with increases in serum bilirubin and renal failure. Brain abscess may be a complication. It may be treated by liposomal amphotericin (*Wade et al., 1995*).
4. **Pneumocystis pneumonia.**

This presents in the first 6 months. It is diagnosed by bronchoscopy and broncho-alveolar lavage. It is prevented by septrin prophylaxis, one tablet daily for the first 6 months post-transplant (*Wade et al.*, 1995).

**G- Malignancies:**

Six per cent of organ transplant recipients will develop cancer, usually within 5 years of the transplant. Many are related to immunosuppression. Malignancies include lymphoproliferative disease, skin cancers, and Kaposi's sarcoma. Hepatocellular carcinoma recur in the graft usually within the first 2 years (*Tan-Shalaby & Tempero*, 1995).

**H- Post-OLT recurrence of HCC:**

In a recent multicenter study by the Milan Liver Transplantation Unit from Italy, a series of 132 patients who underwent OLT for HCC were analyzed. Twenty-one patients (16%) developed a neoplastic recurrence, the majority within the first 18 months after OLT. The commonest sites of recurrence were the engrafted liver, lungs, and bone. Eight of the patients could be salvaged by another resection. Those having resectable recurrences had a 4-year survival of 14%. This study also underscored the importance of stringent patient selection, and the use of multimodal adjuvant therapy protocols to prevent poor long-term outcomes after OLT (*Molmenti and Klintmalm*, 2002).
Image-Guided Tumor Ablation

The term “image-guided tumor ablation” is defined as the direct application of chemical or thermal therapies to a specific focal tumor(s) in an attempt to achieve eradication or substantial tumor destruction. Although tumor ablation procedures can be performed at laparoscopy or surgery, most procedures aimed at treating HCC are performed with a percutaneous approach. Hence, several authors refer to these procedures as “percutaneous therapies”. The concept of image guidance is stressed in the title to highlight that image guidance is critical to the success of these therapies. Over the past 25 years, several methods for chemical or thermal tumor destruction have been developed and clinically tested. More recently, new options that use novel, nonchemical nonthermal ablative techniques have become subjects of clinical investigation. (Brown et al., 2009).

1. Chemical Ablation

The ordinary technique used for chemical ablation of HCC has been percutaneous ethanol injection (PEI). Ethanol induces coagulation necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. An alternate method for chemical ablation is acetic acid injection. However, acetic acid injection has been used by very few investigators worldwide. (Lencioni and Crocetti ,.2008).
A. Percutaneous ethanol injection:

One of the first methods devised to ablate liver tumors involved percutaneous ethanol injection (PEI). Several nonrandomized trials in the 1990s confirmed that PEI can safely achieve complete necrosis of small HCCs, with 5-year survival rates of 32%–38%. However, the technique suffered from the need for multiple treatment sessions, uncertainty of the ablation zone, and a high local progression rate of 17%–38%. Several randomized controlled trials compared PEI versus RF ablation in the treatment of small HCC. These trials demonstrated an approximately 20% advantage for RF ablation versus PEI in overall survival at 3–4 years, mainly as a result of a much lower incidence of local tumor recurrence in the RF ablation group. Also, approximately three fold fewer treatment sessions were required for RF ablation compared with PEI. Two recent metaanalyses comparing RF ablation versus PEI echoed these sentiments declaring RF ablation superior to PEI in the treatment of small HCC. PEI maintains the advantage of allowing treatment of tumors near sensitive organs and tissues, and avoids the problem of the “heat-sink” effect adjacent to vessels. (Orlando et al., 2009).

B. Acetic Acid Injection:

Acetic acid injection has been proposed as a viable alternative to PEI for chemical ablation of HCC. Despite some initial promising reports, this method had limited diffusion and was not tested in large series of patients. The reported survival outcomes are not better than those obtained by several authors with PEI. (Huo et al., 2003).
II. Thermal Ablation

The thermal ablative therapies involved in clinical practice can be classified as either hyperthermic treatments including radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation or cryoablation. The thermal damage caused by heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50°C - 55°C for 4-6 minutes produces irreversible cellular damage. On the other hand, the freezing of tissue with temperatures between -20°C and -60°C followed by rapid thawing results in cell membrane disruption and induces cell death. For adequate destruction of tumor tissue, the entire target volume must be subjected to cytotoxic temperatures. (Lencioni and Crocetti, 2007).

A. Radiofrequency Ablation (RFA):

Surgical resection or orthotopic transplantation should still be considered the gold standard for patients with hepatocellular carcinoma (HCC), with reported 5-year survival rates exceeding 70% in appropriately selected patients. However, surgical resection is only possible in the minority of patients with HCC confined to the liver due to the degree of cirrhosis, the tumor burden, and/or the anatomical location of the tumors. Transplantation is limited by the paucity of donor organs. For non-surgical candidates with no evidence of extra-hepatic disease, radiofrequency ablation (RFA) should be considered as a viable treatment option.
RFA may be delivered from a percutaneous, laparoscopic, or by an open approach based on multiple patient and technical factors. The ideal patients for RFA are cirrhotic patients with small tumors who are not surgical candidates based on their underlying hepatic function. RFA in appropriate selected patients can produce durable long-term survival with minimal procedure-related complications. Combination of RFA with other treatment strategies, particularly transarterial chemoembolization (TACE), can be effectively used to treat patients with advanced multifocal HCC or as a bridge to liver transplantation. As the technique and experience improves, the indications for RFA to treat patients with HCC will likely continue to increase. (Mazzaferro et al., 2009).

**Technical Considerations for Radiofrequency Ablation:**

RFA produces thermal tissue damage through the use of high-frequency alternating currents moving from the tip of an intra-tumoral electrode into the targeted surrounding tissue. The patient is part of a closed loop circuit that includes the RF generator, electrode needle, and grounding pads placed on the patient. Frictional heating of the targeted tissue results from the movement of ions within the tissue following the alternating currents. As temperatures rise above 60° C surrounding the electrode, tissue coagulative necrosis is achieved in the tumor and surrounding hepatic parenchyma. The region of necrosis is relatively consistent with a zone of ablation within the first few millimeters of the electrode–tissue interface. The final size of the ablative region is proportional to the square of the radiofrequency current referred to as the radiofrequency power density.
Early RFA probes were simple straight unipolar needles, limiting the size of the tumor ablated to less than 2 cm in diameter.

These unipolar probes have been replaced with multi-array probes that create a larger region of necrosis. These modern expandable probes have multiple tines that are deployed once the needle electrode is inserted within the tumor. The curved electrodes are then deployed to a desired distance based on the size of the tumor. Reliable tissue destruction can only be expected 5–10 mm away from the multiple array hook electrodes. (Camp et al., 2011).

RFA can be successfully performed via either a percutaneous, laparoscopic, or open approach. Using image guidance from either transcutaneous or intraoperative ultrasonography visualization, the RFA needle electrode is inserted into the targeted tissue and the needle tines are deployed. RF energy is then applied following an established algorithm. Generally, small lesions (<2.5 cm) can be treated with a single deployment targeted at the center of the tumor (Fig.36). Larger tumors (>2.5 cm) generally require multiple deployments to achieve complete tumor necrosis. Strategic deployment of the electrodes is planned so the regions of necrosis overlap to ensure complete tumor destruction. Typically, the most posterior portion is treated first followed by reapplication more anteriorly at 2–2.5 cm intervals within the tumor. A percutaneous approach should be considered for cirrhotic patients with small (<3 cm), early staged HCC tumors especially in the periphery of the liver. Lesions in the dome of the liver are often not accessible from a percutaneous approach. Patients undergoing a percutaneous approach
usually require monitored sedation and are discharged from the hospital within 24 hours of the procedure. *(Camp et al., 2011).*

**Fig.(36):** The upper left image demonstrates the use of intra-operative ultrasound (IOUS) on the surface of the liver to visualize tumors within the hepatic parenchyma. The radiofrequency needle electrodes are placed within the tumor under IOUS guidance. The upper right image demonstrates deployment of the multiple array secondary electrodes within the tumor. For tumors 2 cm in diameter or smaller, a single placement of the multiple array electrode is usually adequate to produce a 4–5 cm diameter zone of coagulative necrosis completely destroying the targeted tumor (lower inset illustration). *(Camp et al., 2011).*

A laparoscopic approach utilizes laparoscopic ultrasonography which has the advantage of improved resolution relative to transcutaneous visualization. Intraoperative ultrasound may better define the location of the tumors and allow more precise positioning of the RFA probes close to major vasculature near a given tumor. This approach is appropriate for patients with no prior history of abdominal surgery and
centrally located tumors less than 4.0 cm in size. Open RFA should be considered for larger tumors (>4.0 cm), multiple tumors, if the tumor is close to major hepatic blood vessels, or if dense adhesions prevent a laparoscopic approach. One major advantage of open RFA is that it allows for temporary hepatic inflow occlusion. This technique may improve the effectiveness in RFA of large hypervascular tumors and tumors in close proximity to major blood vessels by improving the RFA temperature response. Increased blood flow in the targeted RFA region leads to heat loss or a cooling effect limiting the degree of tissue necrosis and, therefore, the effectiveness of RFA. Hepatic inflow occlusion minimizes this cooling effect during RFA application. A second advantage of the open RFA approach is the ability to combine RFA with hepatic resection strategies to address multiple tumors. Tumor position can impact treatment decisions regarding RFA. Tumor not amenable to a margin-negative resection such as tumors abutting the junction of the inferior vena cava and the hepatic veins can often be treated with RFA (Fig.37). Conversely, tumors located in the region of the hilar plate where the portal vein and hepatic artery branches enter the liver should not be treated with RFA. The large bile ducts in this region are susceptible to thermal injury resulting in secondary biliary strictures or fistulas. *(Camp et al., 2011).*
Fig. (37): (a) CT scan image of a hepatocellular tumor abutting the inferior vena cava (open arrows) and the hepatic veins (closed arrows). For adequate ablation, serial deployments of the multiple array electrode probes are necessary beginning just outside of the inferior vena cava, and then sequentially withdrawn to treat the more anterior portions of the tumor. Blood flow through the inferior vena cava and hepatic veins prevents thermal damage of these major vessels. (b) CT scan 6 months after radiofrequency ablation reveals a larger necrotic cavity than the original tumor with patent hepatic veins (closed arrows). (Camp et al., 2011).
Imaging Considerations:

A critical component to the effective use of RFA is preoperative planning and tumor surveillance with appropriate imaging studies. Typically, serial dynamic MRI or multiphasic helical CT scans are used to plan RFA treatment and evaluate response. The goal of RFA is to produce a necrotic cavitory lesion greater in size than the pretreatment HCC lesion when compared by CT/MRI. This comparison is both to assess complete tumor ablation and to evaluate for tumor recurrence. Dynamic MRI or multiphasic helical CT performed during the first 3 months following RFA often demonstrates a hypervascular enhancing rim of inflammatory tissue. This inflammatory response can be difficult to distinguish from tumor recurrence but typically resolves and is usually not evident by scans obtained after the first 6 months. Identifying a local recurrence following RFA can be problematic. Early follow up scans may not be able to differentiate between a recurrence and an inflammatory response. A local recurrence may be detected as progressive local ingrowth of vascularized tissue into the necrotic cavity or as vascularized outgrowth away from the RFA cavity. The arterial phase of a dynamic imaging study is best to identify recurrences because the tumor tissue may appear otherwise isodense with the normal parenchyma. (Paudyal et al., 2007).
Importance of Ensuring a Safety Margin in RFA:

The concept of a ‘safety margin’ has been considered important in RFA for HCC due to:

- ensuring a safety margin is essential to treat microsatellite lesions and compensate for the uncertainty of imaging evaluation.
- local recurrence is inhibited in nodules with an ‘eventually’ achieved safety margin.
- the survival of ‘eventually’ local recurrence-free cases is favorable compared to cases who develop local recurrence.
- the presence or absence of a safety margin in the first treatment is a prognostic factor. *(Kudo., 2010).*

RFA in Combination with Surgical Resection:

RFA has been combined with surgical resection for the treatment of multiple HCC tumors. This combined approach is ideal for patients with bilobar tumors. Using a combined approach, surgical resection can be used for the largest lesion or for segments with the majority of the tumor burden reserving RFA for the preserved liver and smaller residual tumors. *(Camp et al., 2011).*

RFA in Combination with Other Liver-Directed Therapies:

More recently, RFA has been combined with transarterial chemoembolization (TACE) for the treatment of unresectable HCC tumors. TACE embolizes the hepatic arterial branches supplying the tumor with a combination of chemotherapeutic agents and an oily
contrast agent (lipiodol) followed by an occluding agent such as polyvinyl alcohol beads. Performing TACE prior to RFA may decrease the heat loss due to hepatic arterial perfusion enhancing the ablative effects. Reducing heat loss during RFA may allow more effective therapy for larger HCC tumors. In a phase 3 randomized investigation from China, the combination of TACE/RFA was compared with either therapy alone in 291 patients with HCC tumors >3 cm. During a median follow-up period of 28.5 months, median survival for the combination group was 37 months, which was significantly longer than TACE (24 months) or RFA (22 months) alone. For patients with solitary tumors less than 3 cm in diameter, TACE/RFA demonstrated a survival benefit compared with RFA alone. Procedure-related complications were comparably low between treatment groups with five-related deaths (two deaths in the TACE/RFA group and three deaths in the TACE alone group). The investigators attributed the improved results to the altered tumor microenvironment following TACE which enhanced and improved the efficacy of RFA. *(Camp et al., 2011)*.

**RFA as a Bridge Therapy to Transplantation:**

Based on the Milan criteria, appropriately selected patients with either a solitary HCC nodule <5 cm or no more than three tumors each <3 cm in diameter may achieve durable long-term outcomes with liver transplantation. The landmark investigation from Milan, Italy reported 4-year overall and recurrence-free survival rates of 85 and 92% in this subset of patients with HCC. These excellent results have been confirmed by various other institutions.
Unfortunately, the demand for donor livers far exceeds the supply and, in the case of HCC candidates, many patients either die or become ineligible due to progression of disease before a donor liver is available. Bridging strategies have recently been incorporated to slow the progression of HCC allowing more time for donor organs to become available. The successful use of RFA as a bridging strategy to transplantation for HCC has been reported by various institutions. In small series, RFA as a bridging therapy has decreased the dropout rate to less than 15%. Based on a historical control dropout rate of 30%, the use of RFA as a bridging therapy appears advantageous. Although the early experience with RFA as a bridging therapy to liver transplantation appears promising, these results need confirmation in randomized or larger non-randomized trials. (Mazzaferro et al., 2008).

B. Microwave Ablation:

Mechanism and Theoretical Benefits

Microwave ablation refers to the electromagnetic method of inducing tumor destruction by using devices with frequency greater than or equal to a 900 MHz. The rotation of the dipole molecules accounts for the efficient amount of heat generated during microwave ablation. One or more molecules are dipoles with unequal electrical charge distribution and as they attempt to continuously re-orient at the same rate in the microwave’s oscillating electric field, as a result of the microwave transmission the water molecules flip back and forth at a billion times per second, leading to this vigorous movement to produce friction and heat which leads to cellular death via coagulation necrosis.
An additional mechanism responsible for heat generation in microwave ablation is ionic polarization which occurs when ions move in response to the applied electric field of the microwave. The displaced ions cause collisions with other ions converting this kinetic energy into heat. *(Diederich., 2005).*

The current frequencies of the commercially available microwave ablation devices are at either 915 or 2450 MHz. The 2450 MHz is the most commonly adopted microwave ablation device which is the frequency used in the conventional microwave ovens giving the reported most optimal heating profiles. The benefit of the 915 MHz microwave is that it can penetrate deeper than the 2450 MHz microwave which may theoretically yield larger ablation zones. *(Goldberg et al., 2003).*

**Indications**

In general, similar to radiofrequency ablation the indication for microwave ablation should be applied to patients who are not candidates for the more definitive and effective surgical resection. The definition of resectability for hepatocellular carcinoma is quite complex, because in addition to taking into consideration the underlying tumor biology (multiplicity of tumors) the treating physician must take into consideration the health of the non-tumorous liver to ensure that a potential curative resection may be an option. Unfortunately, given the fact that a majority of patients with hepatocellular carcinoma have underlying cirrhosis from either hepatitis B or C, alcohol, or other sources, most patients who have potentially resectable lesions based on the number and location are not surgical resectable candidates based on the lack of health of the non-tumorous liver and the ability of that liver to
withstand that type of resection. Given those limitations, microwave ablation is indicated currently to treat lesions approximately 5.0–7.0 cm in maximum size or less. Most treating physicians would agree that microwave ablation should be utilized in a “curative” indication. These indications or criteria are predominantly defined as a single hepatocellular carcinoma lesion of 6.0 cm or smaller, three or fewer hepatocellular carcinoma lesions with a maximum diameter of 4.0 cm or less and the absence of significant extrahepatic disease, and an expected life expectancy greater than 6 months of survival. Patients in consideration for hepatic ablation must undergo these same extensive pre-evaluations as would patients undergoing hemihepatectomy which should include high-quality dynamic cross-sectional imaging of the liver as well as abdomen and chest, both for ablation planning and for staging of the patients. (Martin et al., 2007).

Choice of Approach

Microwave ablation has been reported to be effectively delivered through an open laparotomy, laparoscopically, percutaneously, and even thoracoscopically in the appropriate patients. Each approach offers its advantages and disadvantages. The current advantages of the percutaneous approach are that it is less invasive and does not require an operation theater to perform the ablation. The potential disadvantage of percutaneous ablation is the inability to evaluate the surface of the liver and inability to evaluate the abdomen for extrahepatic disease. As has been demonstrated in metastatic colorectal cancer, percutaneous ablation has the limitation of understaging patients when relying just on cross-sectional imaging.
The potential advantages of laparoscopic approach are the ability to truly evaluate the hepatic parenchyma, surface of the liver, as well as the intra-abdominal peritoneum for more precise staging. The limitation is that this requires general endotracheal anesthesia as well as an intra-abdominal access which has the potential to be a greater risk for patients with marginal hepatic function. Microwave ablation through an open technique has been reported to be effective also with the ability to combine that technique with radical resection. Use of a combined hepatic resection and ablation technique has been found to be effective and safe in the management of patients with multifocal hepatocellular carcinoma. The ablation technique for microwave ablation is a complex technique requiring the treating physician to have extensive knowledge of the hepatic anatomy, knowledge of the histology of the tumor being treated, extensive knowledge of intra-ablation imaging, and appropriate knowledge for adequate follow-up. Ultrasound is currently the most commonly employed imaging technique because of its convenience and ability to continually allow for real-time evaluation of the ablation. (Robert Martin ., 2011).

**Results**

Despite its encouraging experimental and clinical results, microwave ablation, like other ablative techniques, is still in its evolutionary phase and needs to be standardized. The utility of microwave ablation, as with radiofrequency ablation, is strongly influenced by appropriate patient selection, anatomic location of the tumor(s), physician experience and training, and standardization of
ablation techniques. There still remains a demand for minimum standards for defining ablation success, ablation recurrence, non-ablation site hepatic recurrence, as well as extrahepatic recurrence in order to establish true quality control in this technology. (Diederich, 2005).

C. Interstitial Laser Hyperthermic Ablation:

The term “laser ablation” should be used for ablation with light energy applied via fibers directly inserted into the tissue. A great variety in laser sources and wavelength are available. In addition, different types of laser fibers, modified tips, and applicators can be used. A spherical volume of coagulative necrosis up to 2 cm in diameter can be produced from a single, bare 400-lm laser fiber. Use of higher power results in charring and vaporization around the fiber tip. Two methods have been developed for producing larger volumes of necrosis. The first consists of firing multiple bare fibers arrayed at 2-cm spacing throughout a target lesion, whereas the second uses cooled-tip diffuser fibers that can deposit up to 30 W over a large surface area, thus diminishing local overheating. (Vogl et al., 2002).

To date, few data are available concerning the clinical efficacy of laser ablation, because the treatment has been adopted by few centers worldwide. In particular, no Randomized controlled trials (RCTs) to compare laser ablation with any other treatment have been published thus far. In a recent multicenter retrospective analysis including 432 nonsurgical patients with early-stage HCC, 5-year overall survival was 34% (41% in patients with Child-Pugh class A cirrhosis). (Pacella et al., 2009).
D. Cryoablation:

Cryoablation is based on the cyclic application of extremely low temperatures in the targeted tissue, causing cell death by ice crystal formation. The gradual downsizing of cryoprobes has fueled interest in percutaneous use, which offers several potential advantages versus RF ablation. First, multiple cryoprobes can be used simultaneously to generate a large ice ball. Second, the size and shape of the developing ice ball can be readily visualized using intraprocedural CT, MR imaging, or US. Third, in contrast to heat-based ablation, percutaneous cryoablation is a relatively painless procedure. *(Shimizu et al., 2009).*

Disadvantages

Percutaneous cryoablation faces several disadvantages. The ablation zone of individual probes is generally smaller than seen with RF ablation, and is not aided by an oven effect. The zone of complete lethality lies a variable distance inside the edge of the ice ball 4–10 mm or more meaning a large amount of surrounding hepatic parenchyma must be frozen to ensure a satisfactory treatment margin. Cryoablation can suffer a “cold-sink” effect from adjacent vessels. Finally, there is a concern for high complication risk with cryoablation, including hemorrhage, cold injury to adjacent organs, biliary fistula, cryoshock, and hepatic parenchymal fracture. A prospective trial of intraoperative cryoablation versus RF ablation for liver malignancies showed a much higher complication rate for cryoablation (41% vs 3%). Though cryoablation has some potential advantages over RF ablation, the higher complication rates and the lack of proven efficacy benefit versus other
techniques have caused some authors to question its use in HCC. Further experience with the new, smaller cryoprobes may change this mindset. *(McWilliams et al., 2010).*
III. New Nonchemical Nonthermal Ablation Techniques

New, nonchemical, nonthermal image-guided ablation techniques are currently undergoing clinical investigation. These include irreversible electroporation (IRE) and light-activated drug therapy. These techniques promise to overcome some of the limitations of chemical and thermal-based techniques in the treatment of HCC. (Guo et al., 2010).

A. Irreversible Electroporation:
Cutting Edge Technology:

Irreversible Electroporation (IRE) is a non-thermal, ablation technology designed for precise and effective surgical ablation of soft tissue. The NanoKnife IRE System is the first surgical ablation system based on Irreversible Electroporation technology and represents the next generation in focal ablative therapy. The NanoKnife IRE System enables physicians to treat otherwise difficult to treat parts of the body, near critical structures like vessels and ducts, thereby expanding the physicians' treatment options. (Guo et al., 2010).

Electroporation is a technique that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupting the lipid bilayer integrity to allow transportation of molecules across the cell membrane via nanosize pores. This process, when used in a reversible fashion, has been used in research for drug or macromolecule delivery into cells. IRE is a method to induce irreversible disruption of cell membrane integrity resulting in cell death without the need for additional pharmacological injury. (Lencioni et al., 2009).
The NanoKnife System Parts:

The IRE system consists of two major components: a **Generator** (Fig.38) and needle-like electrical **Probes** (Fig.39). The generator can deliver up to 3000 V of energy in a maximum of 100 pulses which have a maximum pulse length of 100 µseconds. The electrode probe is 19 gauge in diameter and has an active tip that can be exposed up to 4 cm. Two or more monopolar probes or a single bipolar probe must be used at a time. The number of monopolar probes that are used during an IRE procedure is dependent on the size and shape of the desired zone of tissue ablation. The treatment parameter for voltage is dependent on the distance between probes within the targeted tissue. IRE is administered under general anesthesia with administration of atracurium, cis-atracurium, pancuronium, or an equivalent neuromuscular blocking agent to prevent undesirable muscle contraction. *(Lencioni et al., 2009).*
Fig.(38): The NanoKnife generator. (Guo et al., 2010).

Fig.(39): The NanoKnife probe. (Guo et al., 2010).

How NanoKnife IRE System Works:

IRE creates a sharp boundary between the treated and untreated area in vivo. This would suggest that IRE has the ability to sharply delineate the treatment area from the nontreated, and that treatment
planning can be precisely performed according to mathematical predictions. In addition, IRE can effectively create tissue death in microsecond to millisecond ranges of treatment time compared to thermal ablation techniques, which require at least 20 minutes to hours. Moreover, because IRE is a nonthermal technique, there appears to be complete ablation to the margin of blood vessels without compromising the functionality of the blood vessels. Therefore, issues associated with perfusion-mediated tissue cooling or heating (a significant challenge with thermal methods) are not relevant. \textit{(Guo et al., 2010)}.

**Choice of Approach**

Irreversible Electroporation has been reported to be effectively delivered through an open laparotomy, laparoscopically, percutaneously, and even thoracoscopically in the appropriate patients. \textit{(Guo et al., 2010)}.

**The NanoKnife IRE System Benefits:**

Unlike other ablative modalities, NanoKnife IRE System has the potential to expand treatment options available for patients who are not candidates for surgery due to the location which requires treatment.

**Additional benefits include:**

- **Non-thermal:**
  - High voltage pulses permanently open pores in target cell membranes
  - Eliminates heat sink issues
  - Ablate at or near vital structures (e.g., blood vessels, bile ducts, other tissues containing collagen/elastin)
• Potential to spare critical structures—vasculature and ducts remain intact (Fig.40)
• Allows real-time CT/US imaging of ablated zones
• Minimal to no post-procedural pain compared to other traditional modalities
• Ablated tissue removed by the body’s natural processes within weeks:
  – Mimics natural cell death. *(Guo et al., 2010).*

![Image of treated tissue](image)

**Fig.(40):** Following NanoKnife IRE treatment, blood vessels, ducts, and other collagenous structures in the treated area remain viable. *(Guo et al., 2010).*

**B. Light-Activated Drug Therapy:**

Light-activated drug therapy uses light-emitting diodes to activate talaporfin sodium, a small drug molecule which is synthesized from a chlorophyll derivative. Talaporfin sodium has the capacity to concentrate in tumors when administered intravenously. It is then activated by a thin light-emitting activator which is percutaneously inserted intratumorally under imaging guidance.
The drug is capable of absorbing long-wavelength light, resulting in singlet oxygen that causes apoptotic cell death through oxidation and permanent tumor blood vessel closure. *(Lencioni et al., 2009).*
Image-Guided Transcatheter Tumor Therapy

A. Transarterial Chemoembolization (TACE):

Transarterial chemoembolization (TACE) has become the mainstay of treatment for unresectable hepatocellular carcinoma (HCC). Its success is attributable to the ability to deliver high-dose chemotherapy into the tumor vascular bed. The addition of emulsifying agents (i.e., lipiodol) and/or particles to the chemotherapy slows down the blood flow through the tumor blood supply and increases the chemotherapy residence time. Recent technological advances such as drug eluting beads further increase the intra-tumoral drug concentration and residence time, while limiting the plasma concentration. This results in increased tumoricidal effect and less systemic toxicity related to TACE. The survival benefit from TACE has been repeatedly shown to be more than double that of supportive care or systemic chemotherapy alone, with less toxicity. The approval of targeted agents for the treatment of unresectable HCC, such as Sorafenib, can have synergistic effect with TACE on survival. Combination treatments that include TACE, ablation, and systemic maintenance chemotherapy will soon become the standard of care for patients with unresectable HCC. These treatments will also likely result in downsizing of many previously unresectable or non-transplantable patients, a likely benefit but also a challenge to ensure such treatment course is appropriate. Whatever the new standard treatment protocol is for HCC is undoubtedly TACE will play the central role. (Georgiades and Geschwind, 2011).
Vascular Anatomy of HCC:

A number of different cell types are the target of tumor angiogenesis signals, but the final common denominator is the recruitment of vascular endothelial cells resulting in arteriolar and venular angiogenesis and lymphangiogenesis. The increased vascularity is more pronounced on the inflow side of the HCC, which manifests as large, tortuous, and disorganized hepatic arterioles (Fig.41). The increased tumor blood supply can on occasion be so pronounced that results in shunting of blood from the rest of the liver (“sump” effect) or even an angiographically visible shunt between the arterial and the hepatic venous side of the tumor. Interestingly, the pro-angiogenic effect associated with HCC has only a weak effect on the portal venous side leaving the hepatic artery as the main HCC supplier (Fig.42). This phenomenon has therapeutic implications in the field of Interventional Radiology. Transarterial Chemoembolization (TACE) has become the mainstay of treatment for unresectable HCC. During TACE, a catheter is placed in the branch of the hepatic artery supplying the tumor, and high-dose chemotherapy emulsified with ethiodol is infused to near occlusion aided by variable size particle embolization. Since the tumor receives most of its blood supply from the hepatic artery and the normal liver parenchyma from the portal vein, TACE selectively delivers chemotherapy to the tumor while mostly sparing normal liver. In addition, it has long been known based on empirical observations that ethiodol selectively embolizes in the abnormal vascularity of tumors, further increasing the chemotherapy concentration and tumor residence time. The reasons for the tropism of ethiodol toward the tumor vascularity have not been
clarified yet. Figure (43) shows the chemoembolization procedure. Figures (44) and (45) showcase varied responses to treatment which include both Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organisation (WHO) responses. In reality, most HCCs will show both types of response to TACE; however, usually WHO criteria response is more pronounced than RECIST response Table(10).

*(Georgiades and Geschwind , 2011)*.

**Table (10):** Definition of best response according to WHO or RECIST criteria. *(Georgiades and Geschwind , 2011)*.

<table>
<thead>
<tr>
<th>Best response</th>
<th>WHO change in sum of products</th>
<th>RECIST change in sum longest diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all target lesions without any residual lesion; confirmed at 4 weeks</td>
<td>Disappearance of all target lesions; confirmed at 4 weeks</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>50% or more decrease in target lesions, without a 25% increase in any one target lesion; confirmed at 4 weeks</td>
<td>At least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; confirmed at 4 weeks</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Neither PR or PD criteria are met</td>
<td>Neither PR nor PD criteria are met, taking as reference the smallest sum of the longest diameter recorded since treatment started</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>25% or more increase in the size of measurable lesion or appearance of new lesions</td>
<td>At least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or appearance of new lesions</td>
</tr>
</tbody>
</table>
**Fig. (41)**: Vascular supply of HCC. Angiogram just prior to TACE:
(a) performed via a selective microcatheter placed in a branch of the right hepatic artery (black arrowhead) shows the disorganized nature of the hepatic arterioles supplying the tumor (white arrowheads). Post-TACE image (b) shows pooling of the lipiodol–chemotherapy mixture in the abnormal vascular bed of the tumor (arrowheads). *(Georgiades and Geschwind, 2011).*

**Fig. (42)**: Schematic of the vascular supply of HCC. The majority of the hepatic parenchyma blood supply (70–80%) is via the portal vein. Tumor-induced angiogenesis recruits mostly hepatic arterial branches thus HCC supply is almost exclusively by the hepatic artery. Therefore, TACE will preferentially treat the HCC and mostly spare normal liver parenchyma. *(Georgiades and Geschwind, 2011).*
Fig. (43): Transarterial chemoembolization in a patient with unresectable HCC. Coronal T1-weighted, contrast-enhanced MRI image of the liver:
(a) shows a mass in the lower part of the right lobe of the liver (arrows) and a smaller lesion (arrowhead) more cranially. Digitally subtracted, selective, right hepatic arteriogram.
(b) shows the two masses, indicated by arrows (larger) and arrowhead (smaller) to enhance. Post-TACE, coronal, non-enhanced CT image of the liver.
(c) shows the distribution of the lipiodol–chemotherapy mixture to correspond to the larger (arrows) and smaller (arrowhead) masses. Axial, T-1 weighted, contrast-enhanced MRI prior to TACE.
(d) and axial non-enhanced CT of the liver post-TACE show distribution of the lipiodol–chemotherapy mixture within the vascular portions of the tumor (arrows) while sparing the necrotic (devascularized) portions (arrowheads). *(Georgiades and Geschwind, 2011).*
Fig. (44): 50-year-old female with unresectable HCC. Three-month, sequential MRI (a, b, c, d, e) axial images of the liver after TACE. The initially large tumor replacing the entire right lobe of the liver shows gradual response based on RECIST criteria. At last follow-up, 5 years after initial TACE, the residual tumor is a 3 cm calcified nodule in the posterior right lobe of the liver (F). (Georgiades and Geschwind, 2011).

Fig. (45): 34-year-old female with unresectable HCC. Pre-(a) and post-TACE (b), axial, contrastenhanced, MRI images show the tumor (arrows) with mild RECIST response but significant EASL-based response, indicated by significant necrosis. (Georgiades and Geschwind, 2011).
TACE as a Bridge to Transplantation:

Recently there has been considerable interest regarding the role of TACE as a bridge to liver transplantation. It has been postulated that TACE shrinks and/or slows the progression of HCC thus possibly minimizing waiting list drop-off rates. This would theoretically be the case especially for those patients who are barely within Milan or San Francisco transplantation criteria. There is a lack of well-designed, prospective, randomized studies however, and the published ones have thus far been equivocal. One prospective (but not randomized) study showed a 1-, 2-, and 5-year survival after TACE and orthotopic liver transplantation (OLT) of 98, 98, and 93%, respectively, which is better than historical controls, suggesting that pretransplantation TACE does improve survival. The same study, however, concluded that downstaging of patients to within Milan criteria using TACE did not result in any survival benefit. Two other studies have correlated the degree of necrosis with outcome after OLT. One concluded that a high percent of lesion necrosis after TACE predicts lower tumor recurrence rates after OLT, whereas the other concluded that low necrosis rates after TACE “facilitate tumor recurrence.” The latter is unlikely, as there is no teleological effect for TACE. The results above, rather, suggest that good response to TACE indicates favorable disease biology. Overall, the current literature suggests (but is not definitive) that:

1. pretransplantation TACE for patients within but close to falling out of criteria may be beneficial.

2. response to TACE may be predictive of disease biology and by extension, survival after liver transplantation.
Further studies are needed in order to define TACE’s role as a bridge to liver transplant. (Georgiades and Geschwind, 2011).

**B. Chemoembolization with Drug-Eluting Beads (DEB-TACE):**

DEB-TACE is a new drug delivery system that combines local embolization of vasculature with release of chemotherapy into adjacent tissue. Its intended use is for the treatment of hypervascular tumors such as HCC. The administration is similar to conventional TACE, a minimally invasive procedure performed by interventional radiologists. Beads are composed of biocompatible polymers such as polyvinyl alcohol (PVA) hydrogel that has been sulfonated in order for binding of chemotherapy (Fig.46). The beads occlude distal vasculature causing embolization, while the chemotherapy is delivered locally. (Martin and Carter, 2011).

**Fig.(46):** Loading beads. (Martin and Carter, 2011).
**Advantages of DEB-TACE over cTACE:**

The initial pharmacokinetics of both conventional transarterial chemoembolization (cTACE) and DEB-TACE were reviewed in (Varela et al., 2007) and demonstrated that the DEB-TACE is an effective therapy with a favorable pharmacokinetic profile with significantly less systemic doxorubicin exposure when compared to cTACE. Also demonstrated no dose-limiting toxicity for 150 mg per dose therapy, a low peak plasma doxorubicin concentration, and no evidence of doxorubicin-related toxicity. So the results of this study demonstrated the precise delivery of doxorubicin without systemic exposure and thus the theoretical advantage over systemic chemotherapy and conventional chemoembolization (Fig.47).

![Diagram showing drug distribution](image-url)

**Fig.(47):** Drug distribution. (Varela et al., 2007).
Delivery Technique:

DEB administration is performed via angiography. After initial staging 3 Phase CT or dynamic MRI of the liver a planned two to three dose treatment schedule is needed before estimating true clinical response. After the initial treatment, additional treatments are given at 1–2 months, then again at 3–4 months based on patient’s disease, tolerance, underlying hepatic dysfunction, and most importantly, physician assessment of the patient’s overall condition. Treatment dosing and bead size is determined by the extent of the cancer within the liver, A repeat CT or MRI scan 1 month after the last treatment to evaluate response is recommended to decide on future treatments. (Martin and Carter, 2011).

C. Transarterial Embolization (TAE):

Background and Evolution:

In this procedure, an embolizing agent (e.g., Gelfoam, polyvinyl alcohol, acrylic copolymer gelatin particles) is administered intra-arterially via catheter with the goal of completely occluding the tumor-feeding vessels. These agents may produce different effects on vasculature, resulting in permanent or transient occlusion, by acting at different levels in the arterial system. Despite the extensive research that is available on hepatic embolization, the precise effects of embolization on tumor cells remain largely unknown. In fact, recent data suggest that hypoxia, generated by arterial embolization, may activate several genes, including vascular endothelial growth factor (VEGF), leading to compensatory angiogenesis and tumor growth. A direct link among the
degree of embolization, tumor hypoxia, and the stimulation of new blood vessels has been suggested in a number of studies. One study found that blood levels of VEGF were markedly increased in patients who had been treated with embolization. VEGF may also help in predicting treatment response and monitoring disease course after chemoembolization. Moreover, recent research has shown that tumor ischemia and hypoxia may also provide a mechanism for resisting apoptosis. Further, hypoxia has been associated with metastasis and poor outcomes via an unclear mechanism. *(Wu et al., 2007).*

The formation of early revascularization after proximal and temporary embolization induced with Gelfoam has also been described. It seems that the earlier the revascularization of the tumor occurs, the more incomplete the necrosis will be. An occlusion of more peripheral vessels generates a nearly complete tumor necrosis, and current trends in interventional oncology seem to favor distal occlusion. *(Geschwind et al., 2003).*

**Patient Selection:**

TAE is effective as a palliative therapy for unresectable HCC. The selection criteria of patients that may benefit from TAE are similar to those for TACE. TAE has also been used for palliation in patients with hepatic metastases from neuroendocrine tumors and sarcomas. *(Maluccio et al., 2005).*
D. Transarterial Chemoinfusion (TACI):

Background and Evolution:

Transarterial Chemoinfusion (TACI) is a catheter-based intra-arterial therapy that traps high concentrations of chemotherapeutic agents in tumor tissues followed by minimal embolization. TACI with maximally selective catheterization and highly concentrated chemotherapy preparations minimizes the risk of hepatocellular ischemic and cytotoxic complications and maximizes chemotherapy delivered to tumor tissue. TACI with superselective catheterization, although labor intensive, has been shown to be safe. (Ha et al., 2007).

Patient Selection:

The eligibility criteria for TACI are similar to those for TACE. portal venous tumor thrombus (PVT) is not a contraindication. Caution should be exercised to avoid injecting large volumes (more than 10 ml) of lipiodol. Moreover, patients with poor hepatic function and tumors with diameters of more than 9 cm have a high risk of irreversible hepatic failure. (Ha et al., 2007).
E. Intraarterial Infusion Chemotherapy Combined with Interferon:

Background and Evolution:

Although various chemotherapies have been used for the treatment of advanced HCC, it could not play a central role for HCC patients, especially those with liver cirrhosis, because of low sensitivity to the anticancer agents and difficulty in giving a sufficient dose due to poor liver function. However, chemotherapy must be one of the important possibilities of multimodal treatment for advanced HCC, for which hepatic resection and other general therapies would not be effective. The antitumor effects of IFN-α therapy in HCC remain controversial. It is difficult to accurately compare the effectiveness of various therapeutic regimens among different studies because of patient selection bias in liver function or extent of tumor progression and differences in the evaluation methods of the clinical effect. The use of a combination of 5-fluorouracil (5-FU) and Interferon –α (IFN-α) for HCC seemed warranted in view of the association of HCC with HBV or HCV, by virtue of the concurrent antineoplastic and antiviral effects of IFN-α and the potential synergism between IFN-α and 5-FU (Fig.48). (Nagano ., 2010).
### Patient Selection:

Recent studies have indicated the beneficial effects of combined intraarterial 5-FU and s.c. IFN-α therapy (FAIT; fluorouracil arterial infusion and IFN therapy) for intractable HCC with portal venous tumor thrombus (PVTT). For the further advance of HCC treatment and prognosis, this therapy might be a promising treatment modality and is expected to develop. (*Nagano et al., 2010*).

### F. Transarterial Radioembolization:

**Background and Evolution:**

The use of conventional external-beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the cirrhotic liver, that often resulted in radiation-induced liver disease, previously known as radiation-induced hepatitis. Radioembolization is defined as the...
infusion of radioactive substances including microspheres containing yttrium-90 (90Y), iodine-131 iodized oil, or similar agents into the hepatic artery. Currently, the most popular radioembolization technique uses microspheres coated with (90Y), a beta-emitting isotope. Given the hypervascularity of HCC, microspheres injected intra-arterially will be preferentially delivered to the tumor-bearing area and selectively emit high-energy, low-penetration radiation to the tumor. There are currently two commercially available 90Y microsphere devices: Therashpere is made of glass and SIR-Spheres is made of resin. (Kulik et al., 2008).

**Patient Selection:**

The safety of 90Y radioembolization has been documented in several phase 1 and 2 clinical investigations. Because of the minimally embolic effect of 90Y microspheres, treatment can be safely used in patients with portal vein thrombosis. Two absolute contraindications exist for the use of 90Y microsphere treatment. The first includes a pretreatment 99mTc macro-aggregated albumin scan demonstrating significant hepatopulmonary shunting that would result in >30 Gy being delivered to the lungs with a single infusion or as much as 50 Gy for multiple infusions. The second includes the inability to prevent deposition of microspheres to the gastrointestinal tract with modern catheter techniques. Serious complications have been reported as a result of untargeted radiation, including cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, and radiation pneumonitis. (Riaz et al., 2009).
**Systemic targeted therapy**

In 2008, the first large randomized controlled trial demonstrating a significant improvement in survival with a systemic therapy was published. *(Llovet et al., 2008)*.

This trial was terminated early after finding that the median survival was improved from 7.9 months with placebo to 10.7 months with sorafenib, a multikinase inhibitor. It is important to note that the majority of the patients included in this trial had Child A cirrhosis (95%) and good performance status (92%) with advanced tumors (53% extrahepatic spread and 70% macroscopic vascular invasion). Its benefit was subsequently confirmed in an Asian-Pacific population, where there was a higher prevalence of noncirrhotic HCC due to hepatitis B. *(Cheng et al., 2009)*.

This medication is well tolerated with possible serious side-effects including diarrhea, hand–foot skin reaction, hypertension, and hypophosphatemia. There are also ongoing trials to evaluate any benefit of adding sorafenib to other treatment modalities such as resection or TACE. *(Printz., 2009)*.

There have also been several early trials evaluating other targeted therapies for advanced HCC. Bevacizumab, an antivascular endothelial growth factor monoclonal antibody, was evaluated in 46 patients and had a median survival of 12.4 months. *(Siegel et al., 2008)*. Erlotinib, an epidermal growth factor receptor (EGFR) kinase inhibitor, was tested in 38 patients with advanced HCC and showed a median survival of 13
months. When used in combination, the two achieved a median progression-free survival of 9 months and a median overall survival of 15.6 months. (Philip et al., 2005).

Sorafenib is now considered standard of care for most patients with advanced HCC, but current trials have been restricted primarily to patients with Child A cirrhosis and good performance status. Systemic targeted therapy is unlikely to be tolerated or of significant benefit in patients with Child C cirrhosis or poor performance status. Patients with Child B cirrhosis should be treated with caution on an individual basis until larger trials provide more data regarding safety and efficacy in these patients. (Worns et al., 2009).
Progress in stem cell-derived technologies for hepatocellular carcinoma

Currently, efforts are geared towards developing cell-based therapies where hepatocytes and stem/progenitor cells will be used for transplantation into damaged and diseased livers. Such transplanted cells could proliferate and repopulate the liver and eventually restore its functions. (*Skelton & O’Neill .,2008*).

Liver stem cells:

The liver is the only organ in the human body that is capable of renewing itself following the loss of the natural tissue. Even after 70% hepatectomy, this remarkable regenerative capacity is achieved due to the proliferation of hepatocytes and cholangiocytes, and other hepatic cells such as stellate cells, macrophages, and endothelial cells. Under special circumstances, stem/progenitor cells and bone marrow (BM) cells also contribute to this regeneration process. Stem/progenitor cells are critical to the tissue restoration process because they are bipotent and can differentiate into the two primary cell types of the liver, ie, hepatocytes and biliary ductal cells (cholangiocytes). In addition to their role in liver regeneration, stem/progenitor cells are important for studies of organogenesis and liver development. (*Aravalli et al.,2010*).

To date, a number of different types of stem/progenitor cells have been successfully isolated from healthy and injured livers (adult and fetal) as well as from liver tumors. These include cells of human, rodent, canine, swine, and simian origins (Table.11). One such population of
human liver stem cells was recently shown to contribute to the generation of liver parenchyma in severe combined immunodeficient mice. Among liver stem cells, the human hepatic progenitor cells (HPCs) are the best studied. Apart from adult and fetal livers, they have been isolated and characterized from liver specimens with severe hepatocellular necrosis, chronic viral hepatitis, and chronic alcoholic liver disease. In normal adult liver, these cells are localized in biliary ductules (canals of Hering). *(Rao et al., 2008).*

**Table (11):** Liver stem/progenitor cells. *(Rao et al., 2008).*

<table>
<thead>
<tr>
<th>Cell type/name</th>
<th>Species</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human progenitor cells</td>
<td>Human</td>
<td>18, 23, 26, 33, 34</td>
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<tr>
<td>Oval cells</td>
<td>Rat</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td>17</td>
</tr>
<tr>
<td>Stem/progenitor cells</td>
<td>Rat</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>15, 25, 27, 28</td>
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<td>Pig</td>
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<td>16</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>20</td>
</tr>
<tr>
<td>Liver-derived progenitor cells</td>
<td>Human</td>
<td>29, 30, 33–36</td>
</tr>
</tbody>
</table>

**Extrahepatic sources of liver stem cells:**

In addition to these liver-derived stem/progenitor cells, many studies have been published demonstrating that cells of nonliver origin could also differentiate into “hepatocyte-like” cells (Fig 49). These cells
could be a valuable source of hepatocytes and cholangiocytes. It is beyond the scope of this review to discuss every stem cell type that has been described, but those that have been well studied and successfully differentiated into hepatic cell types will be highlighted. \(\text{(Aravalli ,2010)}\).

Figure (49): Intra- and extrahepatic sources of stem cells from different origins that have been demonstrated to differentiate into hepatocyte-like cells. \(\text{(Aravalli ,2010)}\).
I. Bone-marrow derived cells:

Mesenchymal stem cells (MSC) are multipotent stem cells derived from BM aspirates. They can be expanded readily in cell culture and can be induced to differentiate into many different cell types, including hepatic cells. These in vitro differentiated cells can express hepatocyte markers and possess hepatocyte-specific biochemical activities such as albumin secretion, urea production, and glycogen storage. It has been suggested that these BM-derived cells fuse with damaged hepatocytes after transplantation and change their gene expression patterns to that of mature hepatocytes. Furthermore, implanted MSCs protect the liver by secreting soluble factors that possess antiapoptotic and promitotic properties, as shown in experiments with rats where hepatic failure was caused by D-galactosamine. (VanPoll et al., 2008).

II. Embryonic stem cells:

Embryonic stem cells (ESCs) are derived from the inner mass of an early-stage embryo known as the blastocyst. They are pluripotent and can be maintained in cell culture for prolonged periods of time without disturbing their developmental potential. (Heo et al., 2006).

III. Fetal annex stem cells:

Umbilical cord blood contains multiple populations of pluripotent stem cells. Each of these populations can serve as a source of hepatocytes for liver regeneration. For instance, mesenchymal stromal cells isolated from the umbilical cord could be induced to differentiate into hepatocyte-
like cells in cell culture after treating them with hepatocyte growth factor and fibroblast growth factor-4. (Zhang et al., 2009).

Placenta-derived stem cells are another source of hepatocytes. They can be expanded in cell culture for more than 20 populations. (Lorenzini et al., 2008).

Recently, Chien et al. cultured these cells from human placentae, differentiated them into hepatocytes, and examined their hepatocyte specific functions. When compared with ESCs, there are no ethical issues involved in using these cells because the collection of placentae does not harm either the human mother or the infant. (Chien et al., 2006).

**IV. Induced pluripotent stem cells:**

The induced pluripotent stem cell (iPS) is an inducible cell type that can be generated by epigenetic reprogramming following induced expression of certain transcription factors. (Takahashi And Yamanaka, 2006).

**V. Endothelial progenitor/precursor cells:**

Endothelial precursor cells (EPCs) constitute a cell type that has the potential to differentiate into mature functional endothelial cells that form a capillary or line the lumen of a blood vessel. (Nakamura et al., 2007).
VI. Others:

The adipose tissue contains MSCs that are multipotent and can be differentiated into functional hepatocyte-like cells by treatment with a cocktail of cytokines. (Banas et al., 2007).

**Role of stem cells in liver cancer:**

In the normal adult liver, there is little proliferation. However, following partial hepatectomy or injury, hepatocytes proliferate rapidly and repopulate the liver to restore its physical mass and physiologic functions. Initial experiments with rodents have demonstrated the ability of hepatocytes to proliferate and to repopulate the liver mass after partial hepatectomy. The data regarding the ability of human hepatocytes to undergo extensive cell division came from studies on chronic hepatitis with HCV and HBV. (Donato et al., 2002).

Recent studies have demonstrated that the capacity to sustain tumor formation and growth resides in a small proportion of stem cells known as “cancer stem cells” (CSCs). They have a greater colony-forming efficiency, higher proliferation potential, and greater ability to form tumor in animal models. The identification of CSCs in a number of tissues including brain, prostate, breast, myeloid, gastric, colon, and lung reinforced the notion that stem cells might also exist in the liver. CSCs were later identified and isolated from the liver. (O’Brien et al., 2007).
**Stem cell therapy for treatment of HCC:**

Due to the problems associated with orthotopic liver transplantation, transplantation of hepatocytes has been proposed as an alternative treatment option for liver disease. However, widespread use of this approach is severely limited due to the shortage of reproducible sources of hepatocytes. As a result of this, as well as the emergence of the stem cell field, stem/progenitor cells with the capacity to differentiate into hepatocyte-like cells appear to be a promising curative option in liver disease. These cells could regenerate the liver mass because they can proliferate for prolonged periods of time and differentiate into hepatic cells after transplantation. *(Drobinskaya et al., 2008).*

The most important implication of liver CSCs is their potential clinical impact in developing novel therapeutic approaches for HCC. Recently, several groups have reported isolation and characterization of human HCC stem cells. For example, CD133 has been reported to be a marker of CSCs in various tissues (brain, pancreas, prostate, colon) and to identify CSCs in hepatocellular carcinoma cell lines. They found that HCC was hierarchically organized and originated from a population of progenitor cells that expressed CD133+. These progenitor cells also possessed characteristics similar to that of normal stem cells and the ability to self-renew and differentiate. In a follow-up study by the same researchers, it has been shown that CD133+ HCC stem cells were the cell population responsible for the chemotherapy (doxorubicin and 5-fluorouracil) resistance seen in HCC, and could be the source of tumor recurrence after chemotherapy.

They also demonstrated that CD133+ HCC cells survived chemotherapy significantly better than most tumor cells which did not
express CD133, and that the underlying mechanism was the constitutive activation of the serine/threonine protein kinase Akt and Bcl-2 cell survival pathways. An obvious clinical implication of this finding is the fact that specific inhibitors of these pathways would potentially be useful in the treatment of HCC. (Ma et al., 2008).

Advances in stem cell technology provide opportunities to develop novel approaches with an ability to reduce the morbidity and mortality associated with liver cancer. Liver cancer is a multifactorial disease with many different underlying pathogenic mechanisms caused by a variety of risk factors. Despite enormous progress during the past several decades, patient survival remains very low. Prospective, randomized human clinical trials are expensive, time-consuming, and very difficult to perform. A severe shortage of livers for orthotopic transplantation has compounded this problem even further. Unfortunately, hepatocyte transplantation has achieved little success in humans so far and there is a greater need to isolate and enrich stem cells with greater clonogenic potential to use them for therapy. (Alison ., 2005).

However, stem cell therapy for the treatment of liver cancer is a long way away from reality. Rather than using treatments such as tetrosine, which are clinically unacceptable, enhancing the clonogenic potential of stem/progenitor cells isolated from healthy livers might prove critical for creating novel cancer therapeutics. Towards this goal, a better understanding of the molecular mechanisms involved in tumor formation and progression, development of new antifibrotic agents, experimental animal models that closely mimic the human disease, and antiviral agents are critical for the success of cell-based therapies for liver cancer. (Aravalli ., 2010).
PATIENTS AND METHODS

This prospective study was conducted in General Surgery department, Benha University and National liver institute, Menofia University from Sept. 2011 to Oct. 2013 on 60 patients.

Patients were diagnosed to have HCC based on typical radiological features of HCC by two imaging techniques (US and spiral contrast enhanced CT) plus or minus alpha fetoprotein level higher than 400ng/ml.

Inclusion criteria:

• Solitary HCC smaller than 5 cm in diameter.
• No extra-hepatic metastasis.
• No radiological evidence of invasion into the major portal/ hepatic vein branches.
• Good liver function with Child Class A, with no history of encephalopathy, ascites refractory to diuretics, or variceal bleeding.
• Platelet count of >50,000/mm3 and prothrombin activity higher than 60%.
• No previous treatment of HCC.
• Patient generally fit for either surgical resection or local radiofrequency ablation therapy.

Patients were randomized into 2 groups:

• Resection group (n=28 patients) assigned to undergo hepatic resection.
• Radiofrequency group (n=32 patients) assigned to undergo radiofrequency thermal ablation.

Written informed consent was obtained before surgery from all patients after explanation & discussion of the procedure and its possible complications.
All patients were subjected to:

- History taking
- Thorough clinical examination including hepatomegaly, splenomegaly or ascites.

**Laboratory investigations:**

Hepatitis viral markers, complete blood count, liver function tests and serum alpha fetoprotein.

**Imaging studies:**

- Abdominal ultrasound for assessment of hepatic focal lesion: site, size, number, echopattern, and detection of splenomegaly or ascites.
- Colour-Doppler detection of intralesional arterial signal.
- Spiral contrast-enhanced CT to detect hepatic lesion with contrast uptake in early arterial phase and rapid wash-out in late venous (portal) phase

**Resection Group:**

During the study period, 28 patients (subdivided into patients with HCC < 3cm and patients with HCC > 3cm - < 5cm) were submitted to surgical resection of HCC. Resection aiming at a free resection margin of at least 1 cm over the tumour by visual estimation was performed intraoperatively.

All surgical resections had negative resection margins confirmed with histopathology. Surgical specimen examination confirmed the presence of liver cirrhosis in all patients. Nonanatomic resections were performed in 17 cases, in the other 11 cases anatomic resections were performed [four lefts lateral lobectomy (segments 2,3); five bisegmentectomies (segments 5,6); and two segmentectomies (segment 5)].

Anatomic resection was defined as resection of the lesion together with the portal vein branch related to the lesion and the corresponding hepatic territory. Nonanatomic resection was defined as resection of a lesion without regard to segmental, sectional, or lobar anatomy.
Patients & Methods

Surgery was carried out under general anaesthesia using a bilateral subcostal incision. Formal abdominal exploration was done to exclude other intra-abdominal pathology.

After mobilization of the lobe with the lesion, attention was then turned to the porta-hepatis which was dissected, followed by extrahepatic pedicle occlusion of the respective portal and hepatic artery branch in anatomic resections.

In nonanatomic resections hilar dissection was omitted and direct parenchymal transaction along an estimated plane 1 cm over the tumour using scalpel or cutting current diathermy after application of bipolar radiofrequency device (which consists of 2x2 array of needles arranged in a rectangle, introduced perpendicular into the liver along the intended transection line producing coagulative necrosis of liver parenchyma and sealing biliary radicles and blood vessels); or using ultrasonic activated scalpel with application of hemostatic sponge over the raw liver surface to assure haemostasis. Ligation of the Intra-parenchymatous pedicles was routinely done in all cases.. Suction drains were left after hepatic resection, Fig 1-9.

RFA Group:

During the study period, 32 (subdivided into patients with HCC < 3cm and patients with HCC > 3cm - < 5cm ) were submitted to RFA with percutaneous approach under ultrasound guidance in an room setting under conscious sedation .Subcostal approache was used patient was in an anti-Trendelenburg position.

Either 3 or 5cm expandable electrode needles, according to tumour size, with multiple retractable lateral-exit J-hooks on the tip were introduced into the centre of the tumour enabling a substantial and reproducible enlargement of the volume of thermal necrosis produced with single needle insertion and offer the potential of large volume coagulation necrosis. RF thermal ablation was performed with a gradual increase in power until either the power roll off was
achieved or 15 minutes of treatment time had elapsed. Thermal coagulation of the track was performed during needle withdrawal.

Immediately after the procedure, sterile dressings were applied on the site of puncture; the patients were asked to lie down on the site of puncture for at least 2 hours with observation of vital signs every half an hour.

**Assessment of patients after treatment and follow up:**

HCC treatment was ended when the entire tumour appeared echogenic with ultrasound and disappearance of intralesional arterial Colour-Doppler signals with the next strategy of follow up:

- Abdominal ultrasound to detect the change of echopattern of hepatic focal lesion, one week after treatment, 1 and 3 months later then every 6 months.
- Spiral CT one month after treatment, response was considered complete if there is no contrast enhancement of hepatic lesions in arterial phase and partial if there were areas of enhancement within the original lesion.
- Serum alpha-fetoprotein 3 months later and every 6 months.

The morbidity, hospital stay, overall survival, and disease-free survival for both groups were accounted. Psychological and physical welfare of the patients were assessed on a 4-point (4: normal, 3: partially disturbed, 2: disturbed and 1: distressing) questionnaire of three subscales including: physical wellbeing; relational life and psychological well-being; and total psychological and physical welfare.

**Statistical analysis:** The collected data were tabulated and analyzed using t-test Chi-square test and Z test. Statistical analysis was conducted using the SPSS (Version 16) for Windows statistical package. Values of P<0. 05 were considered significant.
**Patients & Methods**

Fig. (50) HCC in right lobe of the liver (segment VI)

Fig. (51) Marking of resection Line with diathermy
Patients & Methods

Fig. (52) Radiofrequency device used 1cm away from the margin of the tumor for haemostasis

Fig. (53) Cutting through the liver parenchyma using scalpel
Patients & Methods

Fig. (54) Cutting through the liver parenchyma using scissor

Fig. (55) The dissected tumor with 1cm safety margin before complete excision
Patients & Methods

Fig. (56) Cut surface of the liver after resection

Fig. (57) Resected specimen
Fig. (58) Cut surface of resected specimen
RESULTS

The study comprised 60 patients; 49 (81.6%) males and 11 (18.3%) females, with mean age 45.2±9.6, range 26-67 years. There was a nonsignificant difference (P>O.05) between patients enrolled in both groups as regards the age and sex presentation, with a significant (P<O.001) male predominance in either group. The characteristics of the patients submitted to the study are reported in [Table 1].

In the early post-operative period; transient liver failure was reported in 5 patients, 2 (10.7%) in resection group and 2 (6.2%) in RFA group, they were responded to conservative treatment; mild pleural effusion in 4 patients, 1 (3.6%) in resection group and 3 (9.37%) in RFA group; bile leak in 2 (7.1%) patient in resection group; hepatic abscess in 2 (6.25%) case in RFA group; and wound infection in 2 (7.1%) patients in resection group. There was non-significant difference (P>0.05) in both groups as regards the morbidity (28.57% in resection group versus 21.87 % in RFA group).[Table 2].

The mean hospital stay was 7±2.9 in resection group and 1±1.2 in RFA group; with a significant shorter stay (P<0.001) in RFA group,[Table 3].

Patients included in RFA group showed significantly increased scores of psychological and physical welfare compared to resection group (P<0.001).[Table 4].

The 2 years overall survival rates were 82.1% (85% in patients with HCC < 3cm & 75% in patients with HCC>3, <5cm) in resection group; and 68.7% (77.7% & 57.1% in those had HCC of < 3cm &>3,<5cm respectively) in RFA group; with a significant longer survival (P<0.05) in resection group. Also the recurrence-free survival rates at the end of follow up period were 71.4% (75% & 62.5% in cases with HCC< 3cm &>3,<5cm respectively) in resection group; and
59.3% (72.2% & 42.8% in those had HCC of < 3cm & >3, <5cm respectively) in RFA group; with a significant higher recurrence (P<0.05) in RFA group.

Subgroup analysis showed non significant difference (P>0.05) between both groups as regard the 2 years overall survival & recurrence-free survival in tumours less than 3cm. On the other hand, surgical resection was significant superior (P<0.05) to RFA for 2 years overall survival & the recurrence-free survival in subgroup analyses for lesions >3cm, <5cm, [Table 5&6].

### Table 1. Patients’ demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Resection group N = 28</th>
<th>RFA group N = 32</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>44±2.4</td>
<td>44±1.9</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(26-65)</td>
<td>(31-67)</td>
<td></td>
</tr>
<tr>
<td>Sex, Male</td>
<td>21 75</td>
<td>28 87.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Females</td>
<td>7 25</td>
<td>4 12.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Cause of liver cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>17 64.29</td>
<td>19 62.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hepatitis B Virus</td>
<td>3 14.29</td>
<td>8 25</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hepatitis B &amp; C Virus</td>
<td>8 21.43</td>
<td>5 12.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3cm</td>
<td>21 71.43</td>
<td>18 56.25</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;3cm, &lt;5cm</td>
<td>7 28.57</td>
<td>14 43.75</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AFP:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;400ng/ml</td>
<td>12 42.86</td>
<td>18 62.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;400ng/ml</td>
<td>16 57.14</td>
<td>14 37.5</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Mean(x-)±SD*
**Results**

Graph (1): Comparison between resection group and RFA group regarding sex

Graph (2): Comparison between resection group and RFA group regarding cause of liver cirrhosis
Graph (3): Comparison between resection group and RFA group regarding tumor size

Graph (4): Comparison between resection group and RFA group regarding AFP
### Table 2. Complications for each method

<table>
<thead>
<tr>
<th></th>
<th>Resection group N = 28</th>
<th>RFA group N = 32</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Wound infection</td>
<td>2</td>
<td>7.14</td>
<td>0</td>
</tr>
<tr>
<td>Liver failure</td>
<td>3</td>
<td>10.71</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic abscess</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Biliary leak</td>
<td>2</td>
<td>7.14</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>3.57</td>
<td>3</td>
</tr>
<tr>
<td>Cutaneous Metastasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intra-abdominal Bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>28.57</td>
<td>7</td>
</tr>
</tbody>
</table>
Graph (5): Graph showing complications of resection group.

Graph (6): Graph showing complications of RFA group.
Table 3. Early outcome

<table>
<thead>
<tr>
<th></th>
<th>Resection group</th>
<th>RFA group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 28</td>
<td>N = 32</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>0</td>
<td>0</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Complications</td>
<td>8</td>
<td>7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hospital stay(days)*</td>
<td>7±2.9</td>
<td>1±1.2</td>
<td>&gt;0.001</td>
</tr>
</tbody>
</table>

Mean(X-)±SD*

Graph (7): Comparison between resection group and RFA group regarding Early outcome
Table 4. Psychological and physical welfare scores among studied groups

<table>
<thead>
<tr>
<th></th>
<th>Resection group N = 28</th>
<th>RFA group N = 32</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical well-being</td>
<td>2.78±0.67</td>
<td>3.86±0.38</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Psychological well-being</td>
<td>3.1±0.78</td>
<td>3.7±0.49</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Psychological and physical Welfare</td>
<td>2.78±0.75</td>
<td>3.76±0.44</td>
<td>&gt;0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD

Graph (8): Comparison between resection group and RFA group regarding Psychological and physical welfare
Results

Table 5. Overall patients’ survival rates during the following up period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>28</td>
<td>26</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>92.8</td>
<td>89.3</td>
<td>82.1</td>
</tr>
<tr>
<td>Resection (N=28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>31</td>
<td>27</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>%</td>
<td>96.4</td>
<td>84.4</td>
<td>75</td>
<td>68.7</td>
</tr>
<tr>
<td>RFA (N=32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC&lt;3cm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection (N=20)</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>No.</td>
<td>100</td>
<td>95</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>RFA (N=18)</td>
<td>18</td>
<td>16</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>No.</td>
<td>100</td>
<td>88.8</td>
<td>83.3</td>
<td>77.7</td>
</tr>
<tr>
<td>HCC&gt;3cm,5cm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection (N=8)</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>No.</td>
<td>100</td>
<td>87.5</td>
<td>87.5</td>
<td>75</td>
</tr>
<tr>
<td>RFA (N=14)</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>No.</td>
<td>92.8</td>
<td>78.6</td>
<td>64.3</td>
<td>57.1</td>
</tr>
</tbody>
</table>

Graph (9): Comparison between resection group and RFA group regarding Overall patients’ survival rates.
Table 6. Recurrence-free survival rates during the following up period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable Details</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Resection (N=28)</td>
<td></td>
<td>27</td>
<td>96.4</td>
<td>22</td>
<td>78.6</td>
</tr>
<tr>
<td>RFA (N=32)</td>
<td></td>
<td>28</td>
<td>87.5</td>
<td>22</td>
<td>68.7</td>
</tr>
<tr>
<td>HCC &lt;3cm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection (N=20)</td>
<td></td>
<td>20</td>
<td>100</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>RFA (N=18)</td>
<td></td>
<td>17</td>
<td>94.4</td>
<td>14</td>
<td>77.7</td>
</tr>
<tr>
<td>HCC &gt;3cm,5cm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection (N=8)</td>
<td></td>
<td>7</td>
<td>87.5</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>RFA (N=14)</td>
<td></td>
<td>11</td>
<td>78.6</td>
<td>8</td>
<td>57.1</td>
</tr>
</tbody>
</table>

Graph (10): Comparison between resection group and RFA group regarding overall Recurrence-free survival rates.
DISCUSSION

The management of hepatocellular carcinoma on cirrhosis involves nowadays many treatment options in relation to the tumour stage and the severity of underlying chronic liver disease (El-Serag et al., 2004). Among these, liver transplantation has the best results in terms of overall survival and disease-free survival, but only few patients can be submitted to this treatment because of organ shortage (Hashikura et al., 2001).

Currently, liver resection is the gold standard treatment for resectable liver tumours whenever functional hepatic reserve allows it; however it is not possible or appropriate in up to 80% of cases due to a low predicted hepatic reserve in cirrhosis, significant co-morbidity or technical issues related to the location, number or size of the lesions, subsequently other modalities must examined (Mulier et al., 2008).

RFA presents a valid alternative to hepatic resection on many levels, especially by improving the overall survival compared to standard chemotherapy or palliative treatments. Despite this, overall survivals at 5 years still do not match those of hepatic resection and these outcome differences have been attributed to the fact that hepatic resection patients had resectable lesions while those treated by RFA were unresectable. This explanation, which has been taken by some authors to imply that in matched patients, results with hepatic resection and RFA would be similar, that has resulted in some units advocating a randomized prospective trial for resectable lesions. If proven, the advantage of a minimal invasive technique, with the greater preservation of liver, reduced complications and shorter hospital stays would expand the indications considerably (Adams et al., 2006).
In the current study, only patients submitted to surgical or ablative treatment with curative intent were included because the strong prognostic value of complete response of treatment both in surgical therapies and in RFA has been clearly demonstrated (Guglielmi et al., 2007).

Both treatments in this series were confirmed to be safe, with no death occurring in either group. The current study showed a lower incidence of complications in the RFA group. In addition the length of hospital stay was significantly shorter in the RFA group. These results were likely explained by the less invasive nature of RFA compared with surgical resection. Similar figures were reported by other authors (Livraghi et al., 2003).

In the current study, no patient had postoperative haemorrhage in resection group and the rate of biliary leak was also low (7.14%), this could be attributed to effective biliary control as well as blood vessel occlusion with either the bipolar radiofrequency device or the ultrasonic activated scalpel. Also, all our resections were performed without applying Pringle’s manoeuvre and therefore the rate of postoperative liver failure in our series was low; since avoidance of hepatic pedicle clamping prevents ischmiareperfusion injury to the liver, which is known to predispose to postoperative liver failure (Elias et al., 1995). Apart from achieving a low rate of resection specific complications, the rate of overall postoperative complications in this series was 28.5% and is consistent with that reported in other series ranging from 16 to 45% (Romano et al., 2005).
In this study, RFA provided better quality of life-adjusted survival than that observed with resection group. On the other hand (Molinari and Helton, 2009) reported that hepatic resection had better quality of life-adjusted survival as ablation therapy.

There was superior survival benefit for patients undergoing surgical resection as compared with RFA. However, in subgroup analysis of lesions less than 3 cm, there was no significant difference in recurrence-free survival between RFA and surgical resection. This corresponds with the findings of other studies (Hong et al., 2005). Viral hepatitis could contribute to the HCC recurrences and it could influence the overall outcome. According to the results of this study, recurrence was the main reason of death which directly affected the overall survival analyses (68.7% in RFA group and 82.1% in surgical resection group).

The difference of local tumour clearance between the two modalities might be the essential factor that affected recurrence. HCC mainly disseminates through portal and hepatic veins. The tumour embolus could shed in the neighbouring branches of vessels and form the microsatellite (Shi et al., 2004). Partial hepatectomy especially anatomic resection removed at least one cm rim of normal liver parenchyma together with the original lesion macroscopically, and thus theoretically eliminated both the primary tumour and possible venous tumour thrombi. This was impossible to be achieved by any local ablation modalities. Furthermore, in the RFA procedure, repeated insertion and overlapping the ablation areas were necessary when encountering tumours larger than one single session ablative area. Via the guidance of two-dimensional ultrasound, a viable seam could be possibly left undetected in the actual lesion area which existed in a three-dimensional formation during the process of overlaying the ablation sessions. This hypothesis had actually been proved by Toyosaka et al (Toyosaka et al., 1996).
In cases of solitary HCC less than 3 cm, overlaying ablation was usually not necessary because the necrosis area produced by one session of a single-needle electrode was closed to a sphere with a diameter of three cm. The viable tumour nest was consequently hard to survival due to homogeneously heat effect. This might at least in part explain why no significant difference in recurrence-free survival between RFA and surgical resection for HCC less than 3 cm was found (Teratani et al., 2006).

The results in this study were comparable with other series, Chagnon study on solitary HCC measuring less than 5 cm observed similar overall survival with HR and RFA (Chagnon, 2007). In the retrospective study of Hasegawa et al., although for HCC higher recurrence rates were found for RFA, overall survival was similar to HR for tumours less than 3 cm (Hasegawa et al., 2008). Vivarelli et al., showed that percutaneous radiofrequency had a higher recurrence rate than liver resection and a high number of recurrences, 31.6%, developed at the site of the treated tumour (Vivarelli et al., 2004).

It could be concluded that in patients with Child A cirrhosis with solitary HCC less than 3 cm, RFA provided results with nonsignificant difference to surgical resection with the advantages of being less invasive, shorter hospital stay, and better quality of life. While in tumours between 3 and 5 cm, surgical resection was superior to RFA having better overall survival and tumour-free recurrence rate.
Summary and Conclusion

Hepatocellular carcinoma is the commonest primary liver malignancy. Eighty percent of HCCs arise in patients with liver cirrhosis especially due to hepatitis B infection, the commonest cause of HCC worldwide, hepatitis C infection in which the lead-time from infection to HCC may be 25 years or more, alcoholic liver cirrhosis, and haemochromatosis.

The pathogenesis of HCC when associated with liver cirrhosis is related to chronic inflammatory processes within the liver.

The clinical presentation varies depending on the liver disease, in the presence of liver disease, malignant change, in the liver may be marked by rapid deterioration and decompensation with encephalopathy and ascites.

Special investigations for HCC include abdominal ultrasound, helical CT scan, and MRI. Preoperative evaluation of the functional hepatic reserve is done to decrease the risk of postoperative liver failure.

The best treatment for HCC is resection with clear surgical margins, whenever possible. Unfortunately, surgical resection is not often done because the underlying cirrhosis or extrahepatic spread. It is possible to remove as much as (60-70%) of the normal hepatic parenchyma at the liver resection, but the presence of cirrhosis limits the regenerative capacity of the liver.

Liver transplantation has theoretical appeal for patients with HCC because it is not only remove the malignant tumor but also eliminates possible sites of recurrence in the remaining diseased liver, it also provides hepatic replacement in patients who usually have severely limited hepatic reserve.
Other lines of treatment include ablative therapy such as radiofrequency which was recently reported to treat HCC ranging from 1 to 7cm. Transarterial chemoembolization, systemic chemotherapy provided minimal role in treatment of HCC. At last the recent progress in molecular and cell biology will hopefully provide efficient means to treat inoperable liver neoplasms in a not very distant future.

In this study patients with Child A cirrhosis with solitary HCC > 3.0 cm, RFA advantages of being less invasive, shorter hospital stay, and better quality of life. While in tumours between 3 and 5 cm, surgical resection was superior to RFA having better overall survival and tumour-free recurrence.
Reference


**Reference**


يعتبر سرطان الكبد هو الخامس الأعراض الخبيثة على مستوى العالم ومسؤول عن 
وفاة خمسمائة ألف مريض في السنة .
إن التقدم في استخدام الأشعة التشخيصية والانتشار الواسع في برامج تحديد المرض 
في بدايةه في الناس المعرضين لهذا المرض أتاح الفرصة في تحديد الأورام ذات الحجم 
الصغير والذي يمكن معالجته عن طريق استئصال الورم وزراعة الكبد ، واستخدام العلاج 
الموضعي للورم .
تعتبر زراعة الكبد هي العلاج الأمثل عن طريق إزالة كل الورم وأمراض الكبد الكامنة 
ولكن نقص عدد المترعين وتأثيره على قائمة الانتظار لتفاقم المرض يحدد من عدد 
المرضى الذين يمكنهم الحصول عليه لluck استئصال الكبد يعتبر العلاج الأول لمرضى 
سرطان الكبد في عدد من المراكز .

وجود تليف الكبد يزيد من حدوث نزيف أثناء العملية واحتمال حدوث فشل كبيدي بعد 
العملية لذلك هناك العديد من التدخلات الغير جراحية قد ظهرت لعلاج مرضى سرطان 
الكبد ذات الحجم الصغير ولا يمكن إجراء الجراحة لهم مثل حفنة الكحول والتردد الحراري 
والكي بالبريد ، وتركيب قسطرة في الشريان الكبيدي وحق مواد كيميائية ومجملة في القسطرة 
من بين هذه العلاجات يعتبر الترزد الحراري هو الأحسن حيث أنه يعمل بواسطة إخراج 
طاقة حرارية عميقة في أنسيس الكبد المصاب بالورم ويستبعد أنسية الكبد غير مصابة 
بالورم .

إن استخدام الخلايا الجذعية والجينات الموجهة للخلايا الكبدية لابد أن يكون أكثر 
جذبًا للبحث العلمي لأنه الاتجاه الواعد المشرح لعلاج أمراض الكبد في المستقبل .
في هذه الدراسة المرضى الذين يعانون من السرطان في الكبد بحجم أقل من 
30 سم ، العلاج بالكي الحراري يؤدي إلى نتائج لا تختلف عن نتائج الجراحة ، بالإضافة إلى 
هذه المميزات بأن المريض يبقى في المستشفى لمدة قصيرة وأقل تدخلًا من الجراحة . بينما 
المرضى الذين يعانون من سرطان في الكبد بحجم ( 3 5 سم ) العلاج الجراحي يتفوق 
على العلاج بالكي الحراري من حيث معدل الحياة لكل وفترة عدم عودة المرض .
الاتجاهات الحديثة في تشخيص وعلاج سرطان الكبد

رسالة

توظيفة للحصول على درجة الدكتوراه في الجراحة العامة

مقدمة من

الطبيب / محمد سعيد عيسى

بكالوريوس الطب والجراحة - ماجستير الجراحة العامة

الأستاذ الدكتور / محمد مختار الشهاوي

أستاذ ورئيس قسم الجراحة العامة

كلية الطب - جامعة بنها

الأستاذ الدكتور / عادل عبد الغني السمنودي

أستاذ الجراحة العامة

كلية الطب - جامعة بنها

الأستاذ الدكتور / طارق محمد إبراهيم

أستاذ ورئيس قسم جراحة الكبد والقنوات المرارية والبنكرياس

معهد الكبد القومي - جامعة المنوفية

الأستاذ الدكتور / جمال السيد صالح

أستاذ الجراحة العامة

كلية الطب - جامعة بنها

كلية الطب

جامعة بنها - 2014