HEPATOCELLULAR CARCINOMA

Epidemiology

- Hepatocellular carcinoma is the sixth most common neoplasm and the third most frequent cause of cancer death worldwide.
- Most of the burden of disease (80% - 90%) is borne in regions where infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is endemic.
- The most important clinical risk factor is cirrhosis. Approximately 80% of HCCs develop in cirrhotic livers.
- The incidence of HCC increases progressively with advancing age in all populations, with a strong male predominance.

Screening for HCC

Patients at risk for HCC include:

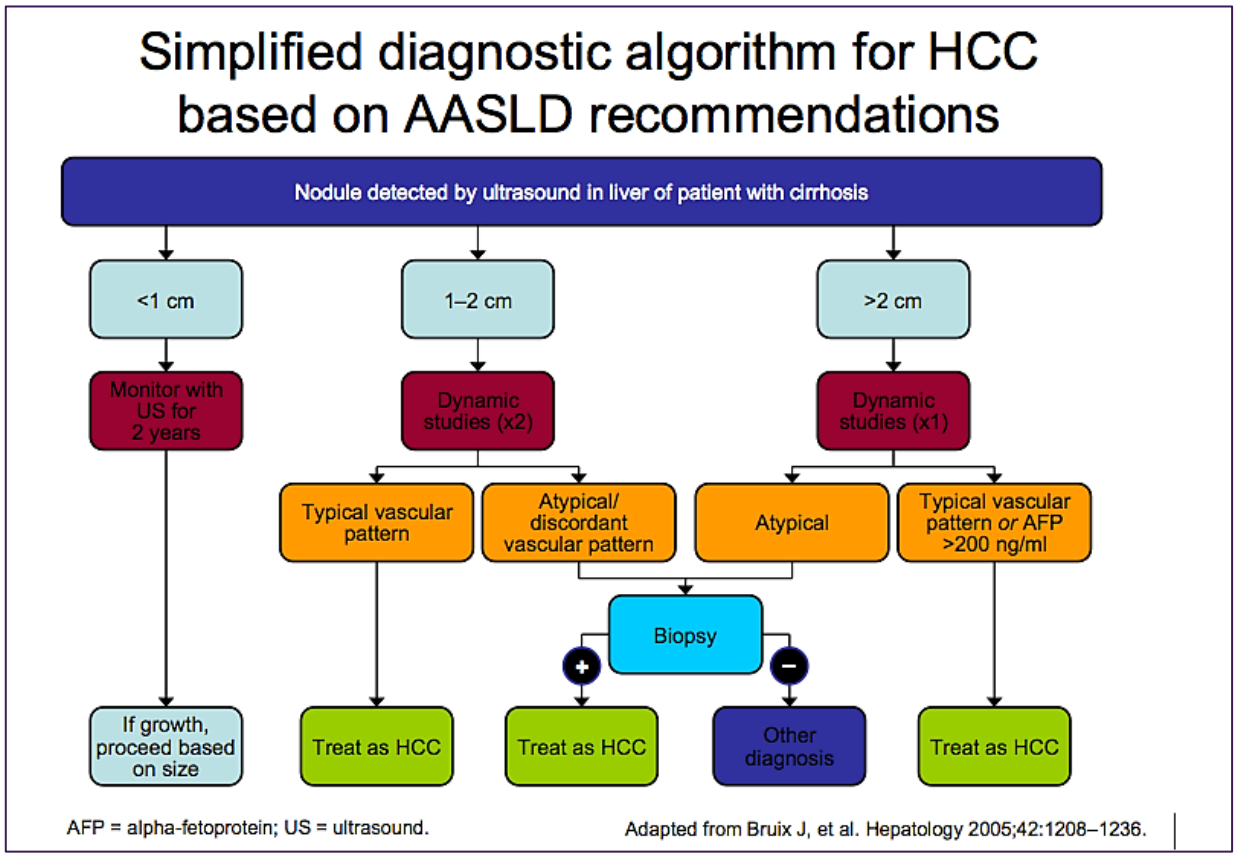
Cirrhosis	Without cirrhosis
• Hepatitis B & C • Alcohol • Genetic hemochromatosis • Non-alcoholic steatohepatitis • Stage IV primary biliary cirrhosis • Alpha -1 antitrypsin deficiency • Other causes of cirrhosis	• Hepatitis B carrier • Hepatitis C

Initial Workup

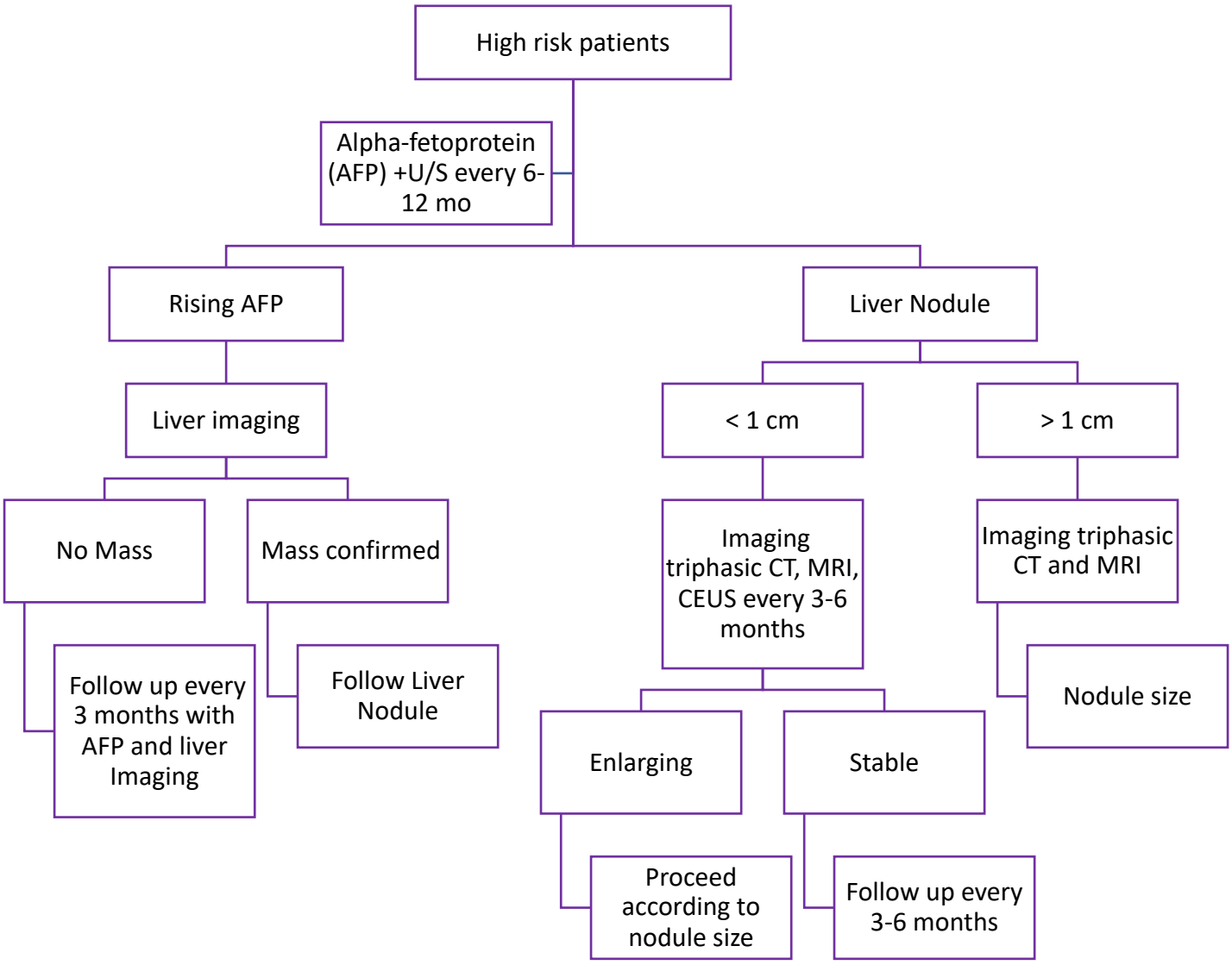
For patients with suspicious liver mass, the initial evaluation should include:

- Full blood workup including:
  - CBC,
  - Serum biochemistry,
  - Hepatitis viral screening,
  - Coagulation profile.
- Alpha-fetoprotein (AFP), diagnostic of primary HCC if:
  - AFP > 4000 ng/ml + HBsAg positive, or
  - AFP >400 ng/ml + HBsAg negative.
- Liver imaging studies (US, CT scan, or MRI) to define:
  - Extend and number of primary lesions
  - The relation to vascular anatomy, and
  - Extrahepatic disease.

- Chest radiograph.
- A bone scan is optional.
- A biopsy may be indicated:
  - If the diagnosis is not confirmed by AFP level or imaging
  - If the patient's PS is not poor
  - If no associated significant co-morbidity and active treatment are possible.
  - If surgery is indicated.
  - During ablative therapy procedures:
    - RFA,
    - Alcohol injection,
    - Trans-arterial embolization,
    - Chemoembolization.



Workup Algorithm



Staging of HCC

- Staging of HCC is important to determine the outcome and planning of optimal therapy and includes:
  - Assessment of tumor extend,
  - Liver function,
  - Portal pressure and
  - Clinical performance status.
- There are many staging systems, including:
  - BCLC (Barcelona Clinic Liver Cancer) staging system,
  - (AJCC) American Joint Committee on Cancer,
  - Okuda staging system,
  - TNM staging system

Child-Pugh Classification of Cirrhosis

Measurements	1 point	2 points	3 points
Bilirubin (umol/L)	< 34	34 -51	> 51
PBC	< 68	68-170	> 170
Prothrombin time	1-4	4-6	>6
Albumin (g/dl)	>3.5	2.8 – 3.4	<2.8
Ascites	None	Mild	Mod-Severe
Encephalopathy	None	G1 or 2	G2 or 4

Class A =	5 - 6 points	Good operative risk
Class B =	7 - 9 points	Moderate operative risk
Class C =	10 – 15 points	Poor operative risk

Okuda Staging of HCC:

Clinical features	0 point	1 point
Tumor size	<50%	>50%
Ascites	Absent	Present
Albumin (g/L)	>3	<3
Bilirubin (umol/L)	<35	>35

BCLC Staging and Treatment Strategy of HCC

	Child-Pugh	PS	Diagnosis	Treatment
0 (Very early)	A	0	Single nodule <2 cm	Resection, ablation, transplant
A (Early)	A-B	0	Single <5 cm or 3 nodules each < 3cm	Resection, ablation, transplant
B (Intermediate)	A-B	0	Large multinodular	Trans-arterial chemoembolization
C (Advanced)	A-B	1-2	Portal invasion, extrahepatic spread	Sorafenib Lenvatinib
D (Terminal)	C	3-4		Best supportive care

Treatment

MDT presentation is critical for an optimal treatment plan, including:

- Hepatobiliary surgeons
- Interventional radiologists
- Radiologists
- Radiation oncologists
- Medical oncologists
- Nuclear medicine

Disease Limited to Liver:

I. Early Stage:

- PS-0
- Child-Pugh A
- No co-morbidity.
  - Solitary tumor less than 5 cm or
  - 3 nodules each less than 3 cm,
  - Preserved liver functions and
  - Good Performance status (PS)

Treatment:

- Discussion with the surgeon and hepatologist [as some patients may meet extended resection criteria.]
- Resection, transplantation, or ablative therapy.
- The 5-year survival exceeds 50%.

II. Intermediate Stage:

- Okuda 1-2
- PS -0
- Child-Pugh A-B

Treatment:

- Survival may reach 50% at 3 years without treatment.
- Chemoembolization or
- Radioembolization or
- Sorafenib or lenvatinib if embolization is not the option
  - (Limited data on sorafenib in Class B, no data for lenvatinib in Class B).

III. Advanced Stage:
• Okuda 1-2 • PS 1-2 • Child-Pugh A-B • Portal invasion • N1M1
Treatment:
• Sorafenib or Lenvatinib   ○ (Limited data on Sorafenib in B Class, no data for Lenvatinib in Class B). • Survival rate of 20% at 3 years.

IV. End-stage Disease:
• Okuda 3 • PS > 2 • Child-Pugh C
Treatment:
• Most patients die within 6 mo. • Best supportive treatment.

V. Extensive Disease:	
• Isolated metastasis	Treat metastasis first

• Patients with:
  ○ PS 0-2,
  ○ Child A-B,
  ○ Bilirubin < 34 umol/L
	Sorafenib or Lenvatinib
	(limited data on Sorafenib in Class B,
	no data for Lenvatinib in Class B).

• Patients with:
  ○ PS > 2,
  ○ Child-Pugh C,
  ○ Bilirubin > 34 umol/L
	Best Supportive Care

Transplantation Criteria:

Transplantation is indicated by a hepatologist and/or hepatobiliary surgeon with the following criteria:

- The patient is not a liver resection candidate.
- Tumor < 5 cm, or 2-3 tumors < 3cm each.
- No macrovascular involvement.
- No extrahepatic spread.

Locoregional Therapy:

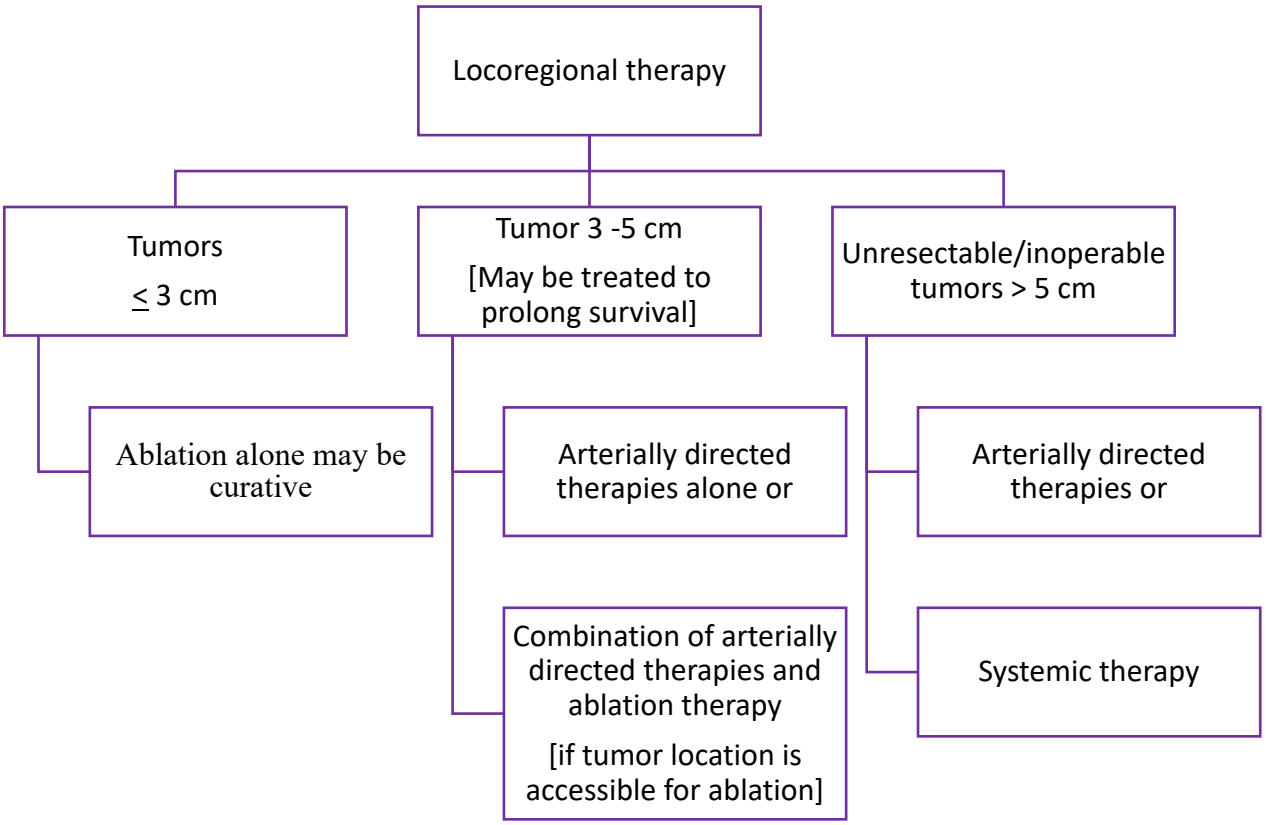
Locoregional therapy is considered for patients who are not a candidate for surgical curative treatment, or as a part of a strategy to bridge patients for other curative therapies. Locoregional therapy includes:

- Ablation therapy
- Arterially directed therapies.

Ablation therapy includes:	Arterially directed therapy includes:
• Radiofrequency ablation. • Cryoablation. • Percutaneous alcohol injection. • Microwave ablation.	• Hepatic artery embolization (HAE). • Trans-arterial chemoembolization (TACE). • Drug-eluting beads (DEB). • Yttrium 90 microspheres (available in KCCC). Lutecium is not available.

All arterially directed therapies are relatively contraindicated in:

- Patients with bilirubin > 51 umol/L (unless segmental injection can be performed).
- Main portal vein thrombosis.
  - (TARE is not absolutely contraindicated, discussion with nuclear medicine specialist is mandatory).
- Child-Pugh Class C.
- Extensive extra-hepatic metastasis.



External Beam Radiation Therapy (EBRT):

- **Stereotactic radiation therapy** is an advanced technique of EBRT.
- Indications:
  - Used as an alternative to ablative or embolization technique when they fail or are contraindicated.
  - Tumor number of 1-3 lesions with cumulative size < 6cm:
    - There should be no extrahepatic spread, or it should be minimal,
    - Child A-B [Child C is contraindicated]

Systemic Therapy:

First-line:	
Sorafenib	Child-Pugh Class A-B7
Lenvatinib	Child-Pugh Class A only

Subsequent lines:	
Regorafenib	Child-Pugh Class A
Cabozantinib	Child-Pugh Class A
Ramucirumab	AFP > 400 ng/mL
Nivolumab	Child-Pugh Class A-B7
Pembrolizumab	Child-Pugh Class A
Sorafenib	Child-Pugh Class A-B7, after 1st-line Lenvatinib

Follow up for patients with HCC:

- Laboratory Investigations:
  - CBC with differential count,
  - LFTs,
  - AFP,
  - Serum biochemistry.
- Triphasic CT scan of abdomen and pelvis, CT scan chest:
  - Every 2 months until stable disease
  - Then every 3 months for 2 years
  - Then every 6 mo for 3 years
  - Then Annually.