Hepatocellular Carcinoma (HCC)

Rahm Makan

HCC Epidemiology

- From western literature
  - Most common primary malignant tumour of liver
  - 5th most common cancer in men
  - 8th most common cancer in women
- Sub-Saharan Africa – HCC under reported and underdiagnosed
- Worldwide incidence is increasing
- Male : female 3.7:1
- 854000 new cases and 810000 deaths p.a.

HCC Aetiology

- Chronic viral hepatitis
  - HBV
    - 25% of carriers develop HCC
    - Accounts for 80% of HCC in Asia and Africa
    - Carriers infected in childhood face 100x lifetime risk
    - High viral load, e Ag positive, genotype c,
  - HCV
- Cirrhosis
- MAFLD
- Chronic alcohol abuse
- Haemochromatosis'
- Alpha -1-antitrypsin deficiency
- Wilsons
- Non-cirrhotic livers are also at risk for HCC

Risk factors for HCC

BOX 96.1 Risk Factors for HCC

MAJOR RISK FACTORS

Chronic HBV infection
Chronic HCV infection
Cirrhosis
NAFLD

OTHER LIVER CONDITIONS

α_1-Antitrypsin deficiency
Hemochromatosis
Membranous obstruction of the inferior vena cava
Type 1 and type 2 glycogen storage disease
Type 1 hereditary tyrosinemia
Wilson disease

INHERITED CONDITIONS NOT ASSOCIATED WITH LIVER DISEASE

Ataxia-telangiectasia
Hypercitrullinemia

OTHER FACTORS

Cigarette smoking
Diabetes mellitus
Dietary exposure to aflatoxin B_1
Oral contraceptive steroid use

Mechanisms HBV causes HCC

- Directly and indirectly toxic
- Postulated mechanisms (Direct)
  - 90% of all patients with HCC have HBV integrated into cellular DNA with random sites of chromosomal insertion.
  - Activation of cellular genes as a result of viral integration
  - Changes in Cellular DNA after viral DNA insertion
  - Transcriptional activation of remote cellular genes due to HBV encoded proteins (X-protein)
  - Activation of JAK/STAT pathways
  - Changes in DNA repair and apoptosis after integration
- Direct link with HBV viral load and HCC risk

Mechanisms HBV causes HCC

- Postulated mechanisms (indirect)
  - Chronic necro-inflammatory disease (cirrhosis)
  - Increased hepatocyte turnover rate due to necrosis and regeneration
  - Distorted architecture of cirrhosis contributes of loss of control of hepatocyte growth
  - Hepatic inflammation leads to formation reactive oxygen species
  - REVEAL study - Genotype C (Taiwan) and F (Alaska) – more associated with HCC

HCV and HCC

- 71 million people with chronic HCC
- All patients with HCV that develop HCC have cirrhotic livers or chronic hepatitis
- Directly carcinogenic , does not integrate into genome
- 5% 5-year cumulative risk of HCC , 7% if cirrhosis
- DAA treatment with SVR regresses fibrosis and risk of HCC. HCC can still occur if already cirrhotic

Cirrhosis and HCC

- Global trend - HCC occurs in cirrhosis 1.3/100 patient years.
- 3.7/100 in HCV
- 2.0/100 in HBV
- 1.0/100 in alcoholic cirrhosis

HCC and Aflatoxin B1

- Derived from fungi aspergillus
- Africa and Asia
- Believed to inactivate third base of codon 243 of TP53 tumour suppressor gene

HCC and other factors

- Haemochromatosis – excess free iron is carcinogenic
- Wilsons
- Alpha -1- antitrypsin
- Hereditary tyrosinaemia
- Type 1 glycogen storage disease
- Membranous obstruction of IVC
- Metabolic syndrome – Diabetes, obesity, NADFLD
- Combined oral contraceptives
- Cigarette smoking
- HIV (associated with viral hepatitis)

BOX 96.2 Key Molecular Pathways Involved in Hepatocarcinogenesis

Angiogenic signaling
Epigenetic promoter methylation and histone acetylation
Growth factor-stimulated receptor tyrosine kinase
JAK/STAT signaling
PI3-kinase/AKT/mTOR
p53 and cell cycle regulation
Ubiquitin-proteasome
Wnt/β-catenin

JAK/STAT, janus kinase/signal transducer and activator of transcription; *mTOR,* mechanistic (or mammalian) target of rapamycin.

Adapted from Roberts L. Emerging experimental therapies for hepatocellular carcinoma: what if you can't cure? In: McCullough A, editor. AASLD Postgraduate Course, 2007. Boston: AASLD; 2007. p 185.

Clinical features of HCC

- Typical symptoms of weight loss, change in general condition, abdominal pain.
- Symptoms usually arise once advanced tumour
- In the setting of cirrhosis, liver may become enlarged, nodular, and irregular with a bruit.
- Ascites = peritoneal and local invasion of IVC

TABLE 96.1 Symptoms and Signs of HCC

Symptom	Frequency (%)
Abdominal pain	59-95
Weight loss	34-71
Weakness	22-53
Abdominal swelling	28-43
Nonspecific GI symptoms	25-28
Jaundice	5-26
SIGN	
Hepatomegaly	54-98
Ascites	35-61
Fever	11-54
Splenomegaly	27-42
Wasting	25-41
Jaundice	4-35
Hepatic bruit	6-25

Paraneoplastic manifestation of HCC

BOX 96.3 Paraneoplastic Manifestations Associated with HCC

Carcinoid syndrome
Hypercalcemia
Hypertension
Hypertrophic osteoarthropathy
Hypoglycemia
Neuropathy
Osteoporosis
Polycythemia (erythrocytosis)
Polymyositis
Porphyria
Sexual changes—isosexual precocity, gynecomastia, feminization
Thyrotoxicosis
Thrombophlebitis migrans
Watery diarrhea syndrome

Paraneoplastic Hypoglycaemia

- Type A – due to glycopenia that occurs in terminal stages due to excessive infiltration.
- Type B – excessive production of pre-IGF-II by malignant hepatocytes, occurs early in disease process.

Other paraneoplastic features in HCC

- Polycythaemia – due to production of erythropoietin factors
- Hypercalcaemia due to parathyroid related peptide.
- Skin – pityriasis rotunda on trunk and thighs

Diagnosis of HCC

- Gold standard is histology.
- Can be diagnosed on imaging – Triple phase CT
- Tumour markers
  - AFP >400ng/ml, levels above 1000 associated with poorer liver transplant outcomes.
  - Other causes of AFP production = germ cell tumours, pregnancy, endoderm tumours, regenerating livers after ALF.
  - Rising trend of AFP is more suggestive.

Imaging of HCC

- Ultrasound – cannot distinguish HCC from other solid lesions therefore used for screening

Imaging of HCC

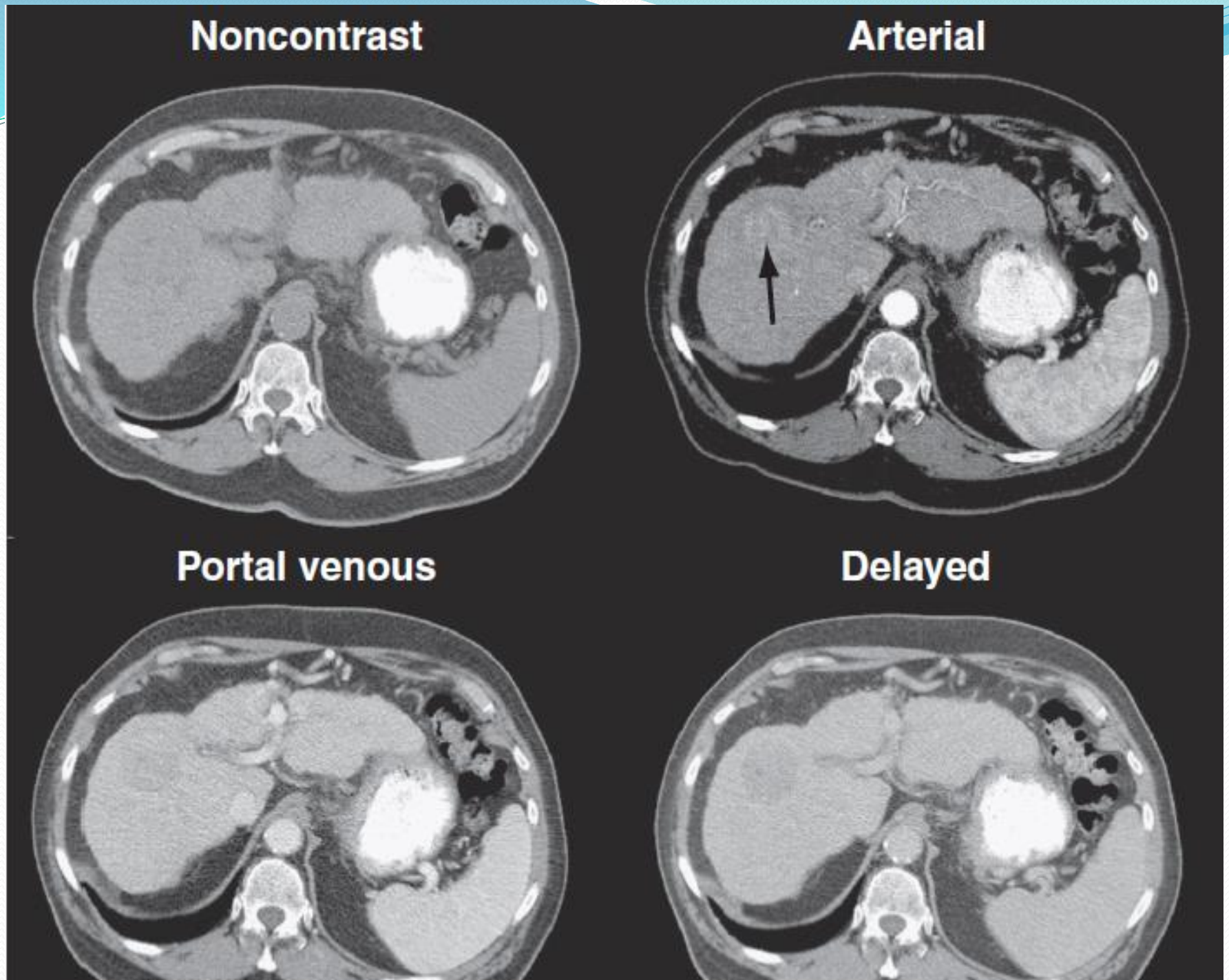
- Dynamic CT (Triple phase CT)
  - Normal hepatic blood supple if from portal vein
  - During neoangiogenesis during shift from low grade to high grade dysplasia, blood supply shifts from portal to arterial supply of tumour. Arterial hyper-enhancement occurs in arterial phase with hypo enhancement in portal venous and delayed phase.
  - If lesion is >2cm, pattern has almost 100% sensitivity
  - LI-RADS

Differential for nodule seen on CT

- Dysplastic nodules
- Arterial portal shunts
- Atypical haemangiomas
- HCC
- Intra-hepatic cholangiocarcinoma
- Confluent fibrosis
- Aberrant venous drainage

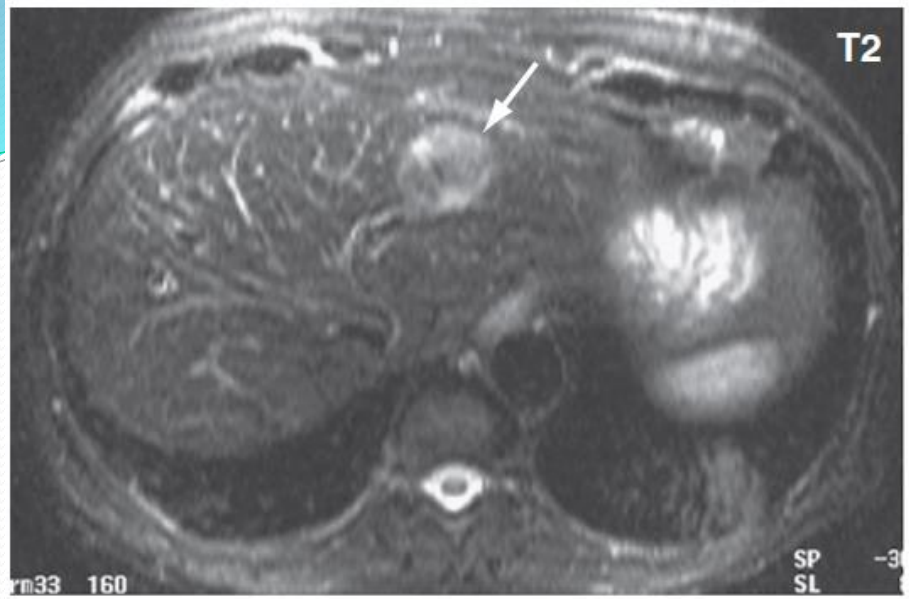
Only HCC and cholangiocarcinoma grows over time.

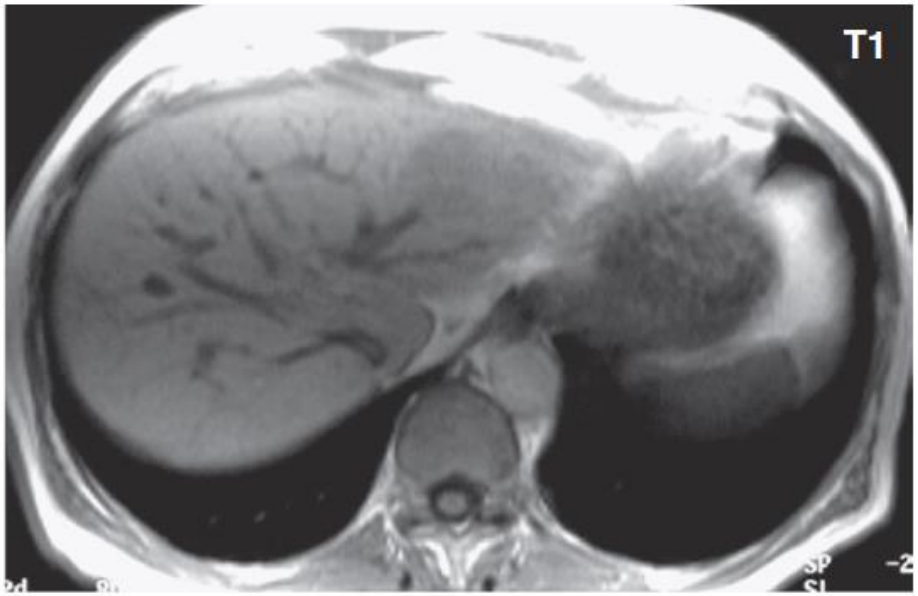
Lesions <1cm without washout pattern can be imaged serially and lesions >1cm should be biopsied.

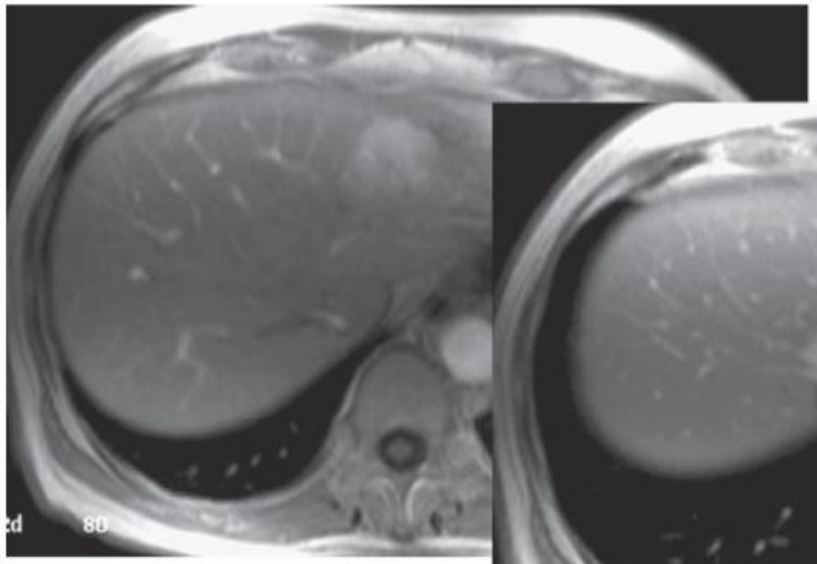

Noncontrast
Arterial
Portal venous
Delayed

Imaging of HCC

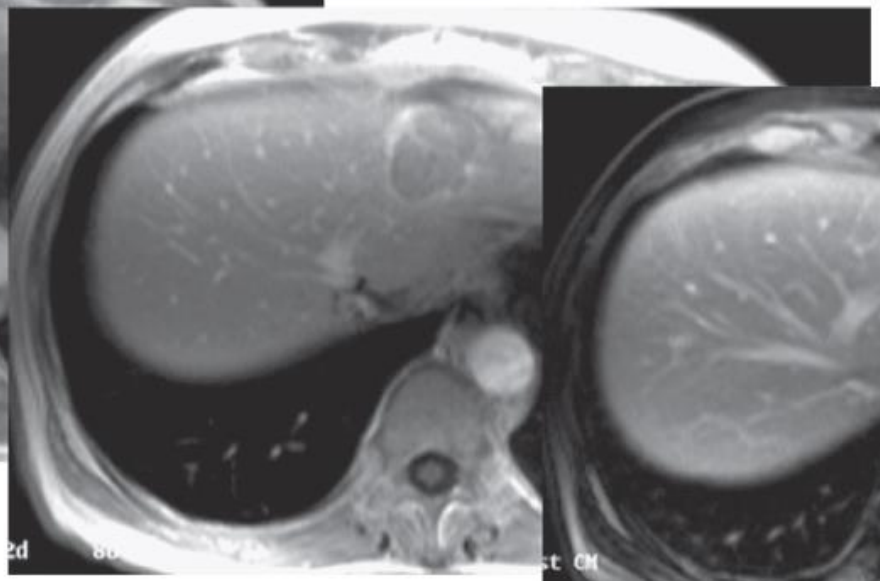
- MRI
  - Gadolinium helps to distinguish HCC from normal liver
  - Sensitivity is similar to CT
  - Findings
    - Hyper intensity on T2 is specific for HCC
    - Hyper intensity on diffusion weighted imaging
    - Lack of enhancement using gadoxetic acid
  - LI-RADS 1-5



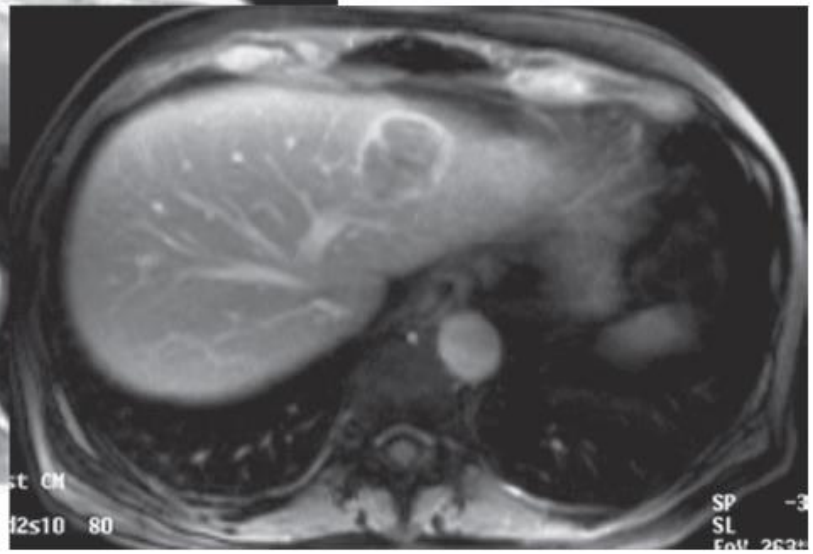




Arterial



Venous



Delayed venous

Imaging of HCC

- PET-CT
  - Less sensitive than CT and MRI, FDG PET can only detect 40% of HCC.
  - Useful for detecting bone metastases
- Hepatic angiography
  - Useful for therapy
  - Chemo/radio/bland embolisation
  - Local chemotherapy
- Laparoscopy
  - Useful for detecting peritoneal or extra hepatic mets.
  - Can perform liver biopsy under direct vision

Histologic features

- Based on ICP – International Consensus Panel
- Immunostaining for GPC3, HSP70, glutamine synthetase, BIRC5 is recommended to differentiate high grade from early HCC.
- Gross appearance
  - Nodular is most common and coexists with cirrhosis – round and irregular nodules
  - Massive - large circumscribed mass, prone to rupture, younger patients with no cirrhosis
  - Diffusely infiltrating – can extend into portal vein

Histologic features

Microscopic features (well differentiated)

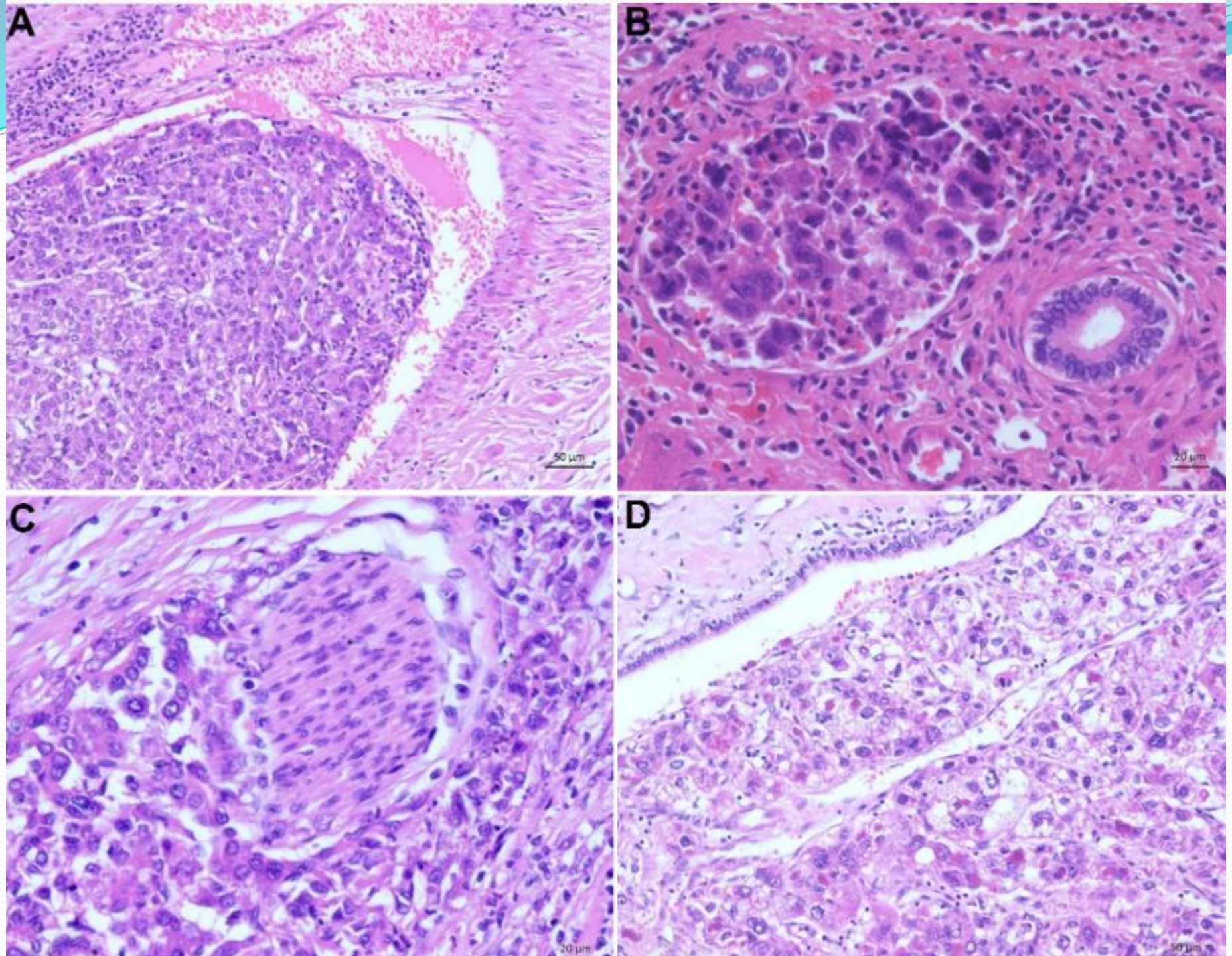
- Bile production is the hallmark of well differentiated HCC
- Varieties
  - Trabecular – Irregular anastomosing plates of cells
  - Acinar – gland like structures present

Histologic features

- Moderately differentiated
  - Solid - cells in masses or nests
  - Sarcomatous
  - Scirrhous – narrow bundles separated by fibrous stroma
  - Clear cell – high glycogen or fat

Histologic features

- Undifferentiated
  - Pleomorphic cells, bizarre giant cells variable in shape. Globular hyaline structures represent the presence of AFP and alpha -1- trypsin (Mallory's hyaline)
- Progenitor cell HCC
  - Progenitor stem cell activation in chronic viral hepatitis and cirrhosis, stain positive for cytokeratin


A
50 µm
B
20 µm
C
20 µm
D
50 µm

METAVIR scoring system

- F0 – no fibrosis
- F1 – portal fibrosis without septa
- F2 – portal fibrosis with septa
- F3 – Numerous septa without septa
- F4 – Cirrhosis

- A0 – no activity
- A1 – mild activity
- A2 – moderate activity
- A3 – Severe activity

Fibrolamellar HCC

- Occurs in young patients
- Equal gender distribution
- Does not secrete AFP
- Not caused by chronic hepatitis B or C
- Occurs in non-cirrhotic liver
- Better prognosis than other HCC

Microscopic

- Plump, deeply eosinophilic hepatocytes surrounded by a fibrous stoma
- Less likely to stain + for GPC3, rather CK7 +

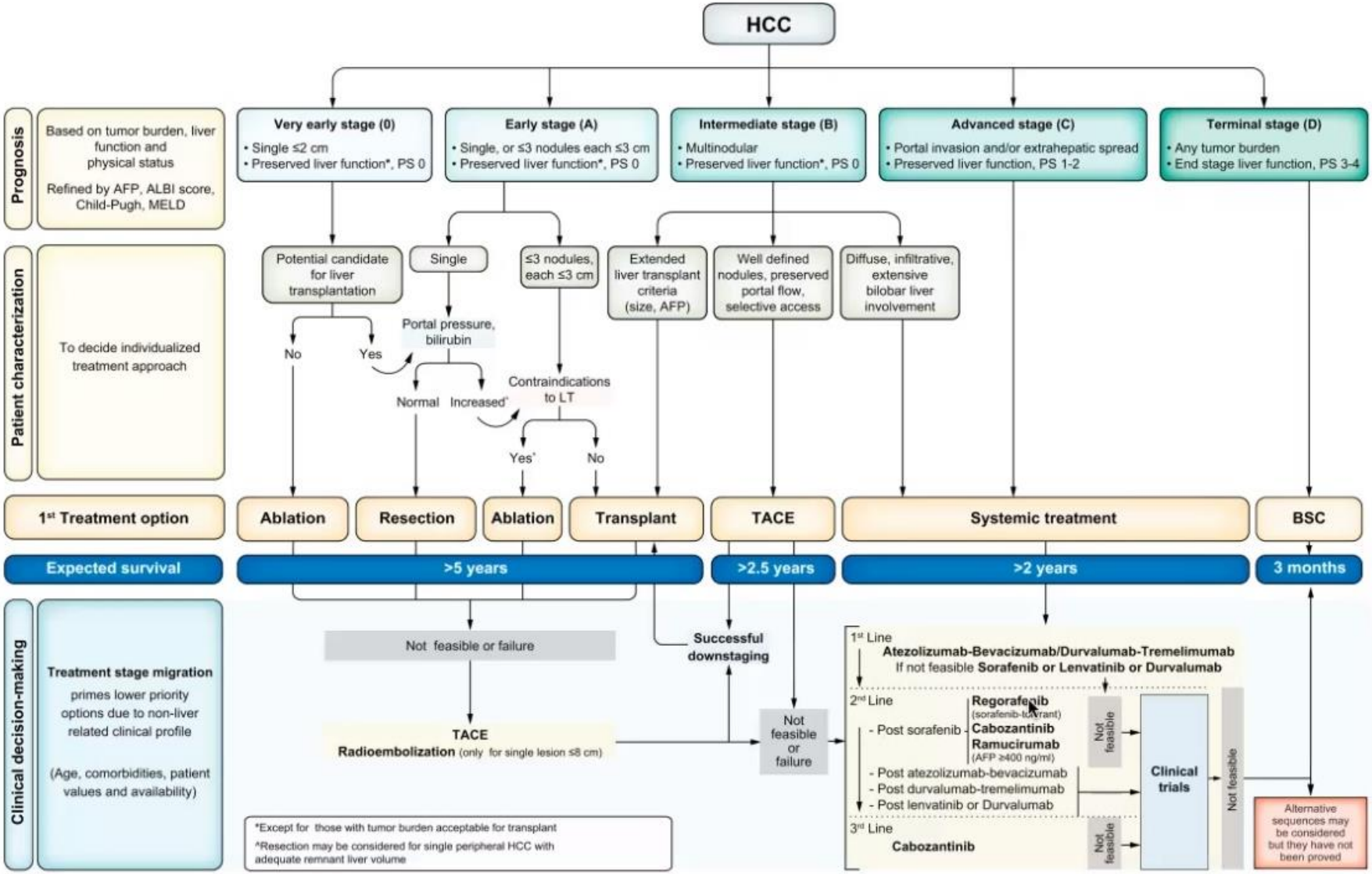
Metastases

- Lungs, lymph nodes and adrenal glands
- 40-57% of patients at autopsy

Staging of HCC

- TNM
- Does not account for existing liver disease
- Many staging systems
- Barcelona Clinic Liver Cancer staging system (BCLC) had best independent predictive power for survival.

Treatment of HCC



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Treatment of HCC

- Very early stage (0)
  - Single <2cm with preserved liver function, normal portal pressures, and bilirubin – resection
  - If liver disease present then transplant
  - If not for LT then ablation
- Early stage (A)
  - Up to 3 nodules all <3cm with preserved liver function, if single with normal portal pressures and bili then resect
  - If liver disease then transplant
  - If liver disease with co-morbid disease then ablate

Treatment of HCC

- Intermediate stage (B)
  - Multinodular with preserved liver function
  - Transplant if extended LT criteria met
  - TACE for down staging then LT
- Advanced stage (C)
  - Portal invasion / extra hepatic spread with preserved liver function
  - Systemic therapy – Atezolizumab, Bevacizumab, Durvalumab, Tremelimumab, Sorafenib, Lenvatinib
- Terminal stage (D)
  - Best supportive care

For optimal surgical resection (>10yr survival)

- One lobe involved, allowing segmental resection
- Child Pugh A
- Normal bilirubin
- No portal HPT
- MELD score < 9

TABLE 96.2 Treatment Options for HCC

Modality	Comments
Surgical resection	Curative but limited to noncirrhotic patients and cirrhotic patients without portal hypertension May be technically difficult High recurrence rate
LT	Successful in selected patients (Milan criteria; see text and Chapter 97) Requires lifelong immunosuppression Expensive and not available worldwide
Radiofrequency ablation or ethanol injection	Potentially curative for small tumors, including multiple tumors High recurrence rate
Transarterial chemoembolization	Prolongs survival in unresectable tumors if hepatic function is preserved; not curative
Chemotherapy	No clear benefit; palliative only Drug toxicity is common
Targeted molecular therapies	Sorafenib is the first such agent shown to improve patient survival Improvement in patient survival with lenvatinib is similar to that with sorafenib Regorafenib, cabozantinib, and ramucirumab (if AFP >400 ng/mL) improve survival after sorafenib failure
Immune checkpoint inhibitors	Nivolumab and pembrolizumab are associated with improved survival after failure of or intolerance to sorafenib

Milan criteria for liver transplant in HCC

- Single tumour < 5cm or 2-3 lesions each less than cm
- No portal/vascular invasion
- No extrahepatic metastases

UCSF down staging protocol inclusion criteria (83.8% @ 5 yr)

- No vascular invasion on imaging
- 1 lesion>5cm but less than 8cm
- 2 or 3 lesions , none >5cm and total tumour diameter of all lesions <8cm
- 4 or 5 lesions, none >3cm , total tumour diameter < 8cm

Liver transplant

- First line for within Milan criteria
- Patients can be down staged to fulfil Milan
- Vascular invasion and mets are absolute contraindication.
- Cadaveric grafts have no contraindication

Local ablation

- Potentially curative for lesions 3-5cm not amenable to resection or transplant due to :
  - Patient choice
  - Number and location of lesions
  - Hepatic dysfunction (Child Pugh B or C)
- Methods – Ethanol, RFA, Microwave ablation

Chemoembolisation

- Used when tumour is not suitable for local ablation due to size, number, location.
- Can be used for down staging

Traditional Chemotherapy

- No survival benefit has been demonstrated
- Response rates less than 20%

Small molecules

- Sorafenib – raf kinase and tyrosine kinase inhibitor of VEGF and PDGF
- Levantinib – multikinase inhibitor of VEGF, FGFR, PDGFR, RET, KIT
- Regorafenib, cabozantinib – multikinase inhibitors
- Nivolumab and pembrolizumab are monoclonal antibodies to the programmed cell death receptor

Novel techniques

- Cryo ablation
- Laser ablation
- External beam radiation
- Yttrium Y-90 microspheres

Surveillance (presymptomatic)

- Ultrasound 6 monthly
- AFP
- In these patients
  - Cirrhotic , child A
  - Cirrhotic, child C awaiting transplant
  - Non-Cirrhotic HBV patients
  - Non-cirrhotic F3 patients
- If nodule found <1cm, follow up is 4/12 for surveillance for first year.
- In non-cirrhotic individuals, surveillance is not economically feasible due to low incidence.

Prevention

- HBV vaccination in childhood and high risk groups
- Coffee consumption has been shown to decrease the risk of HCC in patients with chronic liver disease.
- Prompt treatment after diagnosis for viral hep

Palliation

- Paracetamol upto 3g/day can be used. Avoid NSAIDs
- Radiation for metastatic bone pain
- Avoid Benzodiazepines or use with extreme caution
- Psychology support
- End of life planning.

Other hepatic tumours (for another day)

- Intrahepatic cholongiocarcinoma
- Hepatoblastoma
- Angiosarcoma
- Epithelial Haemangioenthelioma
- Hepatic metastases

References

- Sleisenger and Fordtran. Gastrointestinal and liver disease
- EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.