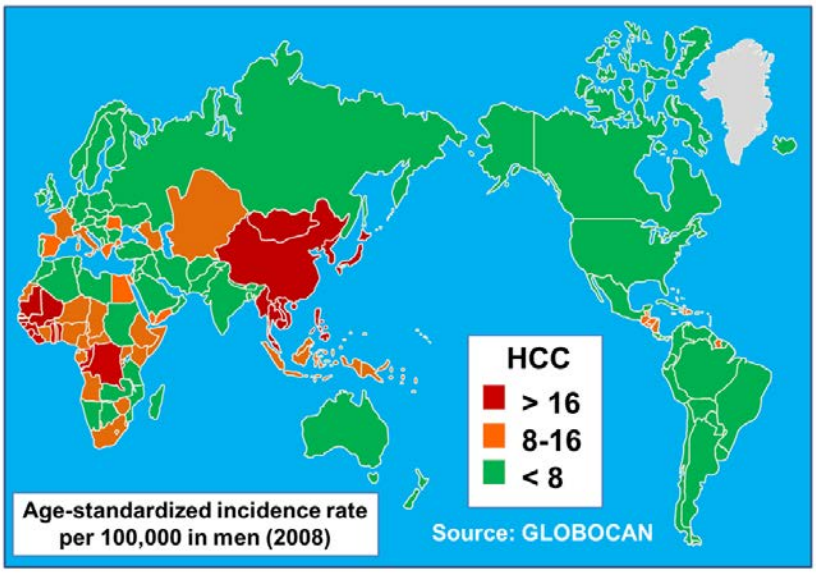
Chapter 13. Primary Liver Cancer

13.1 Hepatocellular Carcinoma (HCC)

- HCC is the 2nd leading cause of cancer related mortality globally
  - 750,000 people worldwide die each year of primary liver cancer
  - More than half of all cases occur in mainland China alone



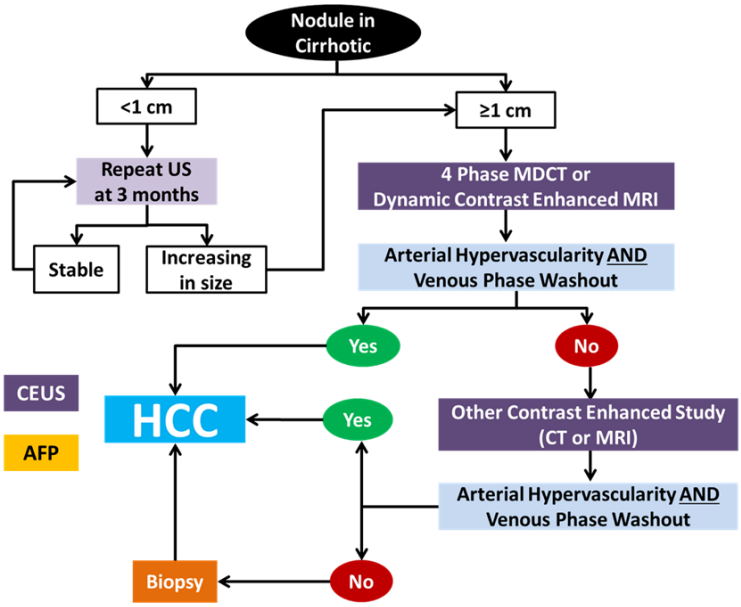
- Globally, hepatitis B virus (HBV) is the leading cause of HCC and the highest prevalence occurs in countries where HBV is endemic
- In North America, hepatitis C virus (HCV) is the leading cause of HCC
  - Most cases of HCC (85%) arise in the setting of cirrhosis, although HCC can develop without cirrhosis (e.g. HBV carrier)
  - Incidence in North America is 6.8 per 100,000 in men and 2.2 per 100,000 in women
  - However, primary liver cancer rates have tripled in men and double in women since 1970 in Canada

Surveillance & Diagnosis

- **Surveillance**
  - **Screening** is the one time application of a test to look for a disease
  - **Surveillance** is a comprehensive program of repeat application of a screening test, with appropriate recall, in an effort to diagnose a disease at an early and asymptomatic stage where effective therapy can be applied
  - HCC surveillance is appropriate in that:
    - A high risk population for development of HCC can be defined (cirrhosis & HBV)
    - Detection of early cancer has more treatment options with better prognosis
    - A single randomized controlled trial from China, which randomized cohorts to surveillance with ultrasound ± alpha-fetoprotein (AFP) versus no surveillance, showed an improvement in overall mortality
  - **High risk populations** in which HCC surveillance is cost-effective
    - **Cirrhosis**
      - Regardless of the etiology
      - Risk varies with etiology (viral > steatohepatitis > other)
    - **Certain HBV carriers (HBsAg +)**
      - Asian males >40
      - Asian females >50
      - Africans >20 (get HCC earlier due to genetics and aflatoxin exposure)
      - Those with family history of HCC

- Surveillance is recommended using ultrasound (US) with or without alpha-fetoprotein (AFP)
  - AFP alone is not recommended for surveillance as it is often negative in early HCC (lacks sensitivity) and it can be elevated during flares of viral hepatitis (lacks specificity)
  - CT and MRI are not cost-effective for surveillance
- Surveillance should be performed every six months (based on cohort and RCTs)
- Follow-up is required if nodules are found on surveillance US (see below)
  - <1 cm repeat US in 3 months (enhanced surveillance)
  - >1 cm order contrast enhanced study for diagnosis

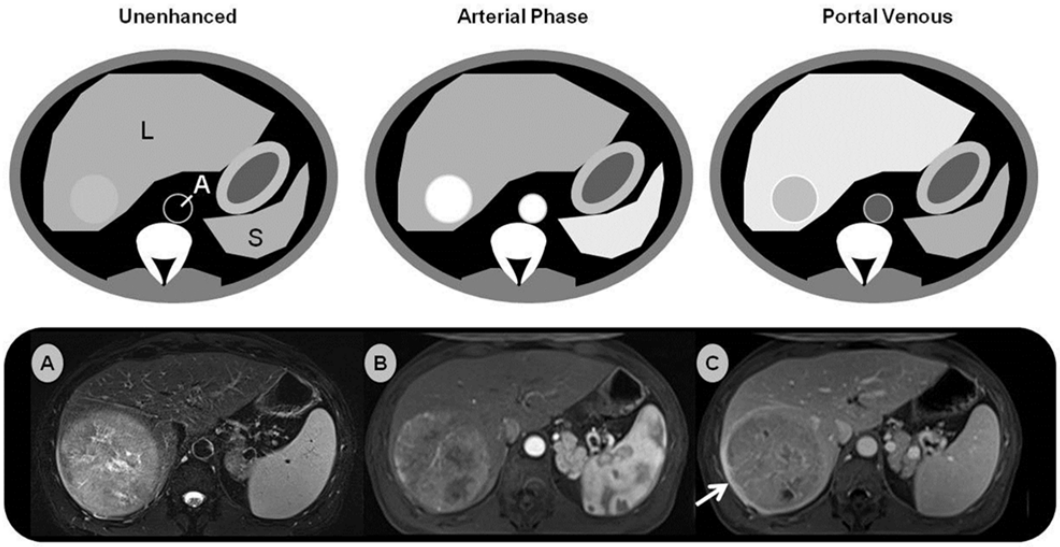
- **Diagnosis**
  - HCC can usually be diagnosed non-invasively without the need for biopsy
  - A contrast enhanced study should be obtained with either multi-detection computerized tomography (MDCT) or dynamic contrast enhanced MRI
  - If the lesion has **arterial phase enhancement <u>AND</u> portal venous washout** then HCC is confirmed and liver biopsy is not required
  - If the imaging is not classic then the other contrast enhanced study should be obtained or if available you can use contrast enhanced ultrasound (CEUS)
    - You require a biopsy only if these studies are negative
  - AFP should be obtained at diagnosis for prognostic purposes (high AFP has poorer prognosis), although it is not required to make the diagnosis (40% don't make AFP)



Adapted from Sherman M, Burak K, et al. Curr Oncol 2011; 18(5): 228-240.

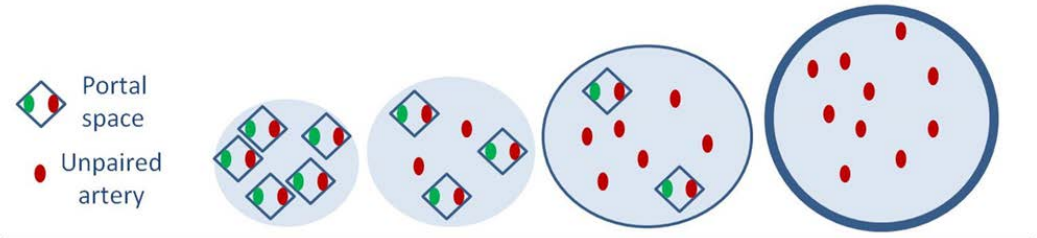
- Contrast enhanced studies take advantage of the dual blood supply of the liver and that as nodules progress from a low-grade dysplastic nodule (L-DN) → high-grade dysplastic nodule (H-DN) → well differentiated HCC (WD-HCC) → moderately differentiated HCC (MD-HCC) they have more of their blood supply from neoplastic arteries with less blood supplied from the portal venous system
  - In an unenhanced study the tumour may be barely visible, but HCC with its rich arterial blood supply will be bright with **arterial phase enhancement** (note that the aorta has contrast on the MRI and spleen is bright with contrast from its arterial blood supply)
  - In the portal venous phase, the contrast from the bowel travels to the liver through the portal vein (80% of the blood supply of the normal liver), but as the HCC has little of its blood supply from the portal vein and the arterial contrast has now left the lesion, it appears darker than the surrounding liver, thus demonstrating **portal venous washout**

- It may have an enhancing capsule (arrow) in portal venous phase



Adapted from Burak KW. Chapter 23: Neoplasms of the Liver. In: First Principles of Gastroenterology & Hepatology. 2012: 463-473.

o The correlation between **pathology** and **radiology** for the spectrum from low-grade dysplastic nodule to moderately differentiated HCC is highlighted here



	IWP class	L-DN	H-DN	WD-HCC	MD-HCC
Pathology	Gross Appearance			Vaguely nodular	Distinctly nodular
	Stromal Invasion	–	–	+/–	+/–
Imaging	Arterial Phase	Iso/Hypo-	Iso/Hypo-	Iso/Hypo- Rarely hyper-	Hyper-
	Portal Venous Phase	Iso-	Iso-	Iso/Hypo- May "washout"	Hypo- or "washout"

Adapted from International Consensus Group. Hepatology 2009; 49(2): 658-64.

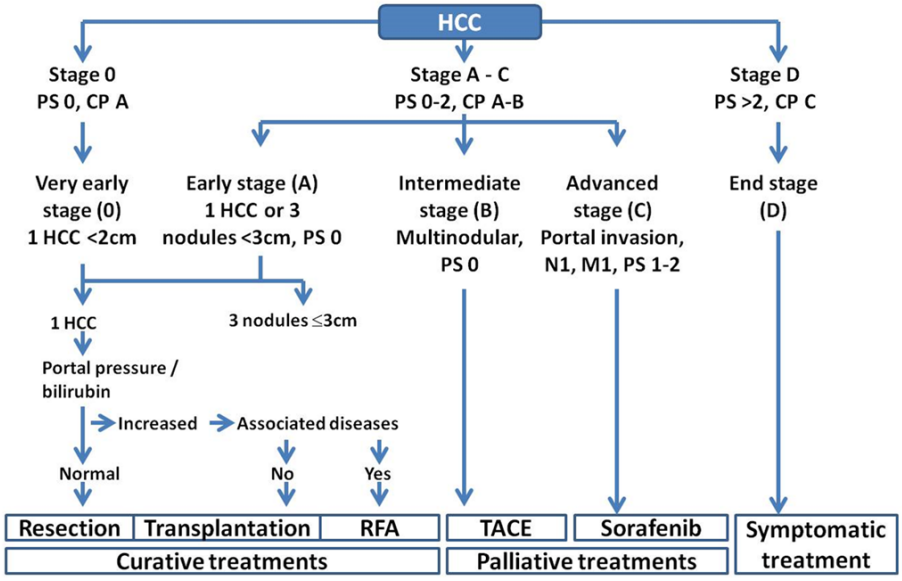
Management

- **Staging**
  - Tumour, patient and liver related factors predict prognosis in HCC
  - **Barcelona Clinic Liver Cancer (BCLC)** staging system is preferred as it uses all three factors – tumour burden, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and liver function using the Child Pugh (CP) class – to predict prognosis and to suggest appropriate therapy based on the best available evidence
    - **Tumour burden**
      - Very early = single <2cm
      - Early = single or three each <3cm
      - Intermediate = multinodular (multiple but confined to the liver)
      - Advanced = portal vein invasion, spread to lymph nodes (N) or metastasis (M)
    - **ECOG PS**
      - 0 = Fully active, able to carry on all pre-disease performance without restriction
      - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work or office work
      - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
      - 3 = Capable of only limited self-care; confined to bed / chair >50% of waking hours
      - 4 = Completely disabled; cannot carry on any self-care; totally confined to bed / chair

- **CP Class** *[see Chapter 14.1]*

	1 point	2 points	3 points
Encephalopathy	None	Controlled	Refractory
Ascites	None	Controlled	Refractory
Bilirubin	≤ 33	34-50	≥51
Albumin	≥36	28-35	≤27
INR	≤ 1.6	1.7-2.2	≥2.3

Class A = 5 or 6 points; Class B = 7 – 9 points; Class C = 10 – 15 points



Adapted from Bruix J, Sherman M. Hepatology 2005; 42: 1208-36.

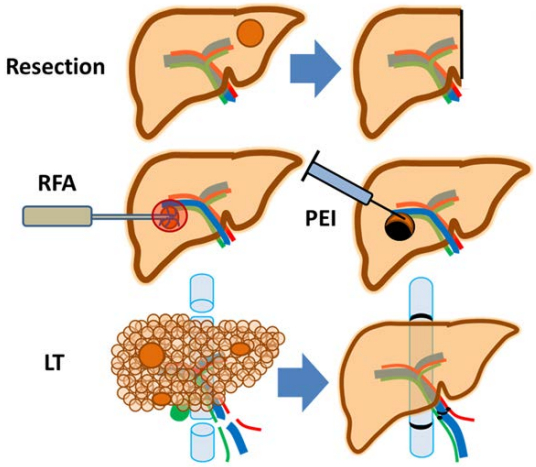
- **Prognosis** depends on the stage and if treatment can be offered
  - BCLC 0 & A (Very Early & Early Stage)
    - 5 year survival of 70% can be seen in patients carefully selected for curative options of resection, radiofrequency ablation (RFA) or liver transplant (LT)

- BCLC B (Intermediate Stage)
  - TACE increases median survival from 16 to 20 months
  - TACE with drug eluting beads (DEB-TACE) can achieve median survival of 4 years

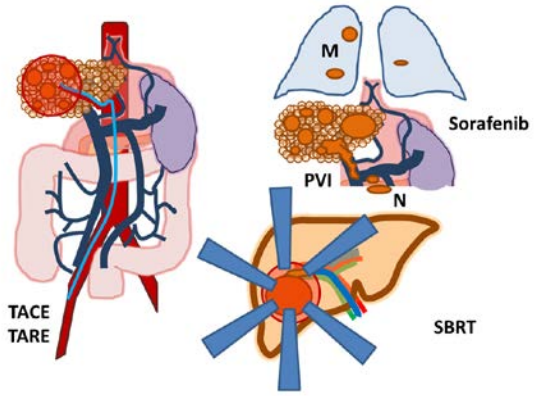
    NOTE: LT can be offered to select patients at this stage in Canada (see below)
- BCLC C (Advanced Stage)
  - Sorafenib was first drug shown to increase survival (from 8 to 11 months)
- BCLC D (End Stage)
  - Survival is < 3 months
  - Patients with Child Pugh class C cirrhosis are end-stage unless LT candidates

- **Treatment**
  - Treatment is recommended according to the BCLC stage
    - **TREATMENT IS COMPLEX AND REQUIRES A MULTIDISCIPLINARY TEAM**

  - **Curative treatment options**
    - Surgical Resection
    - Radiofrequency Ablation (RFA) or Percutaneous Ethanol Injection (PEI)
    - Liver Transplantation (LT)



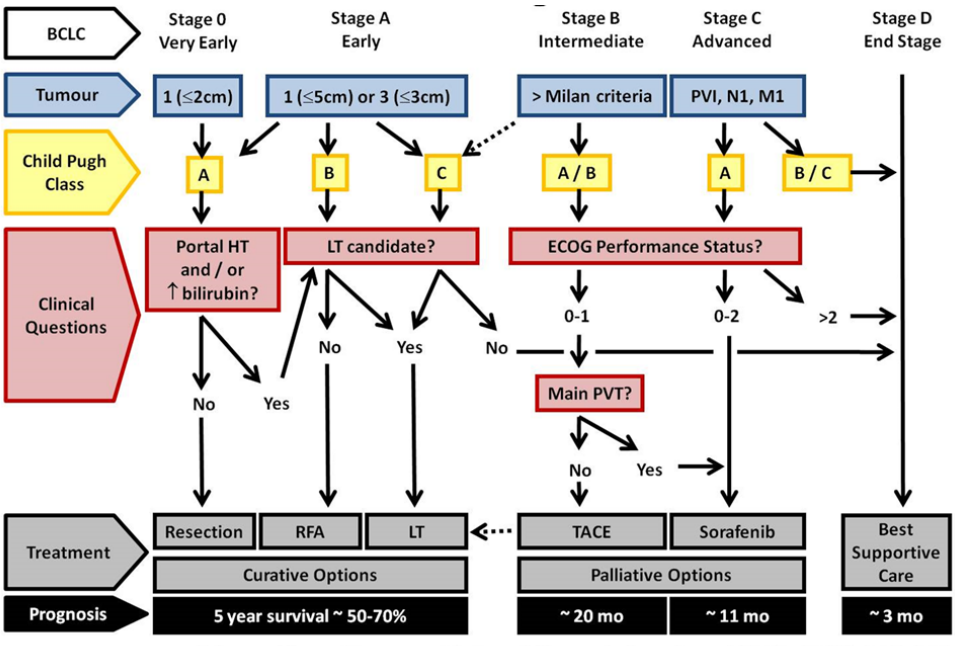
- **Palliative treatment options**



  - Transarterial Chemoembolization (TACE)
  - Sorafenib, levatinib, regorafenib, cabozatinib
  - Transarterial Radioembolization (TARE)
  - Stereotactic Body Radiation (SBRT)

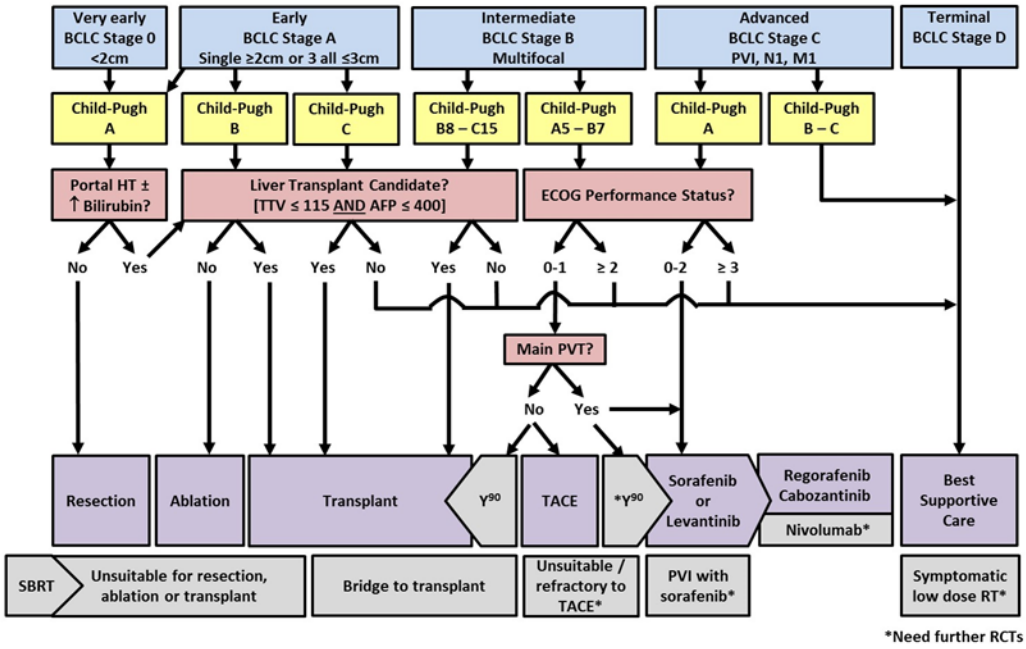
    NOTE: Level of evidence for TARE and SBRT are weaker and therefore are consider experimental

- **Canadian HCC algorithm** uses the BCLC staging system but recognizes that some patients **beyond the Milan criteria** (single tumour ≤ 5cm or three tumours all ≤ 3cm) can undergo LT using TACE as a bridge to transplant (extended criteria)



Adapted from Sherman M, Burak K, et al. Curr Oncol 2011; 18(5): 228-240.

- **Alberta HCC Algorithm** (updated October 2018)



- **Curative Therapies**
  - **Surgical Resection**
    - For BCLC 0 → A but must have preserved liver function (Child Pugh A) with no significant portal hypertension (no varices, hepatic venous pressure gradient or HVPG <10 mmHg, platelets >100) and a normal bilirubin to avoid post-op liver failure
    - Recurrence occurs in 70% at 5 years
    - RCTs vs RFA show similar survival but fewer recurrences after surgery
    - Complications include post-op infections and liver failure (2% mortality)
  - **Ablation (RFA or PEI)**
    - For BCLC 0 → A but lesions should be <3cm and there should be < 3 lesions
    - Can be performed in Child Pugh A or B (those who are not candidates for surgery)

- Meta-analyses of RCTs show that RFA is better than PEI for local control & disease free survival if tumour >2cm but PEI is preferred if concerns about thermal injury to adjacent structures or proximity to blood vessels where heat-sink can be an issue with RFA
- Recurrence also 70% at 5yrs (>2.5 cm predicts recurrence)
- Complications in 2-5% → bleeding, thermal injury, abscess, tumour seeding (1%)

o **Liver Transplantation**

- For BCLC A [and selected B]
- LT is the only therapy that treats both the HCC and underlying cirrhosis, so it can be done in Child Pugh C
- **Milan criteria [single <5cm, 3 HCC <3cm]** predicts low risk for recurrence (<15%)
- Extended criteria has been adopted in Canada where patients can be transplanted up to a total tumour volume (TTV) of 115cm^3 ($4/3\pi r^3$) as long as the alpha-fetoprotein (AFP) is less 400ng/mL **[TTV115 & AFP400]**
- Patient require long-term immunosuppression, which has many complications *[see Chapter 15]*, and organ donor shortage lead to many patients progressing beyond accepted criteria while waiting for LT
- TACE, TARE and RFA are used to prevent waitlist drop-out and bridge to LT

- Palliative Therapies

o **TACE**

- For BCLC B (multifocal) and early stage patients who are not candidates for RFA (tumour too large or in poor location) or to bridge patients to liver transplant

- Takes advantage of the rich arterial blood supply of tumours to provide chemotherapy (usually doxorubicin) with embolic particles (induces tumour ischemia)
- Need to have good liver function (CPA or CPB7) to prevent liver failure from ischemia, and must avoid if there is a main portal vein (PV) thrombosis (↑ chance of liver failure)
- Meta-analysis of RCTs have shown a survival advantage
- Use of drug eluting beads (DEB-TACE) provides a more standardized technique and is better tolerated (but more expensive)
- Complications include post embolization syndrome (fever, nausea, vomiting) in 25-60%, ischemic complications and rarely liver failure (2-3% mortality)

o **Sorafenib**

- For BCLC C (advanced stage) due to malignant portal vein invasion (PVI), lymph node involvement (N1) or metastases (M1) or intermediate stage patients who are failing TACE or who are not candidates for TACE
- Targeted oral chemotherapy with anti-VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor), RAF kinase activity
- RCTs have shown a survival benefit over placebo in patients with preserved liver function (Child Pugh A)
- Side-effects include nausea, diarrhea, hand & foot skin reactions and hypertension

o **Levatinib**

- Blocks VEGF receptors, FGF (fibroblast growth factor) receptors, PDGF receptor, RET, and KIT

- Found to be non-inferior to sorafenib in large open-label phase 3 study (median survival 14 months for levatinib vs 12 months for sorafenib) with high tumour response rates
- Side-effect profile similar to sorafenib

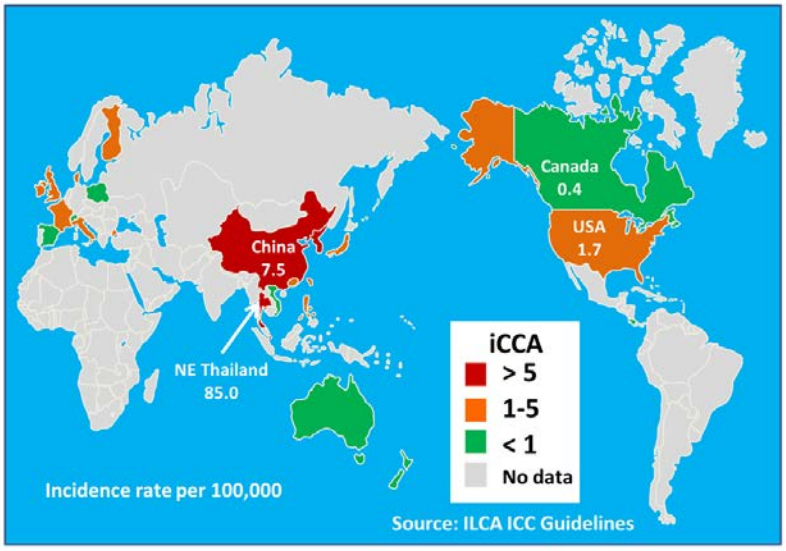
- **Second-line chemotherapy** (failing sorafenib)
  - **Regorafenib** improved survival from 8 months (placebo) to 11 months
  - **Cabozantinib** improved survival from 8 months (placebo) to 10 months
- **TARE**
  - For BCLC B → C (being studied with sorafenib in RCTs)
  - Like TACE it should be reserved for CPA or CPB7
  - Yttrium^{90} (Y90) microspheres provide internal radiation to the tumour
  - Particles are smaller and less embolic → can be used if PV thrombosis or invasion
  - Cohort studies and small RCTs show similar results to TACE, with higher response rates
  - May be better than TACE for large tumours and for bridging patients to LT
  - It is more expensive than TACE and requires two angiograms (first to calculate shunt fraction to lungs and to embolize collaterals) but it can be done as an outpatient as post embolization syndrome is uncommon
  - Complications include radiation damage to liver, lungs or GI tract
- **SBRT**
  - For BCLC A → C (being studied with sorafenib in RCTs), who aren't candidates for other therapies but should be reserved for CPA or B
  - Provides confocal external radiation in 5 fractions

- Cohort studies show good local control
- Complications include radiation damage to liver (one third have deterioration in CP score after SBRT)

13.2 Intrahepatic Cholangiocarcinoma (iCCA)

Epidemiology

- Rare liver cancer (compared to HCC) but its incidence is increasing
  - Incidence in Canada is 0.4 per 100,000
  - Highest rates in northeast Thailand



- **Risk factors**
  - Cirrhosis
  - Chronic viral hepatitis
  - Primary sclerosing cholangitis
  - Alcohol abuse
  - Diabetes
  - Obesity

Surveillance & Diagnosis

- Surveillance is controversial
  - Carbohydrate antigen 19-9 (CA19-9) is a tumour marker but it lacks sensitivity and specificity
  - Treatment options are less beneficial than with HCC

    NOTE: cirrhotics (highest risk group) should already be getting US surveillance for HCC
- **Diagnosis**
  - MRI or CT shows liver mass with arterial phase enhancement
  - CEUS can show early and rapid washout (also seen with metastases)
  - FDG-PET scan may be positive and can demonstrate lymph node involvement or metastases
  - CA19-9 or carcinoembryonic antigen (CEA) tumour markers may be high (may help predict prognosis) but are not always helpful with diagnosis
  - Pathology is required to establish the diagnosis and immunohistochemistry can be helpful

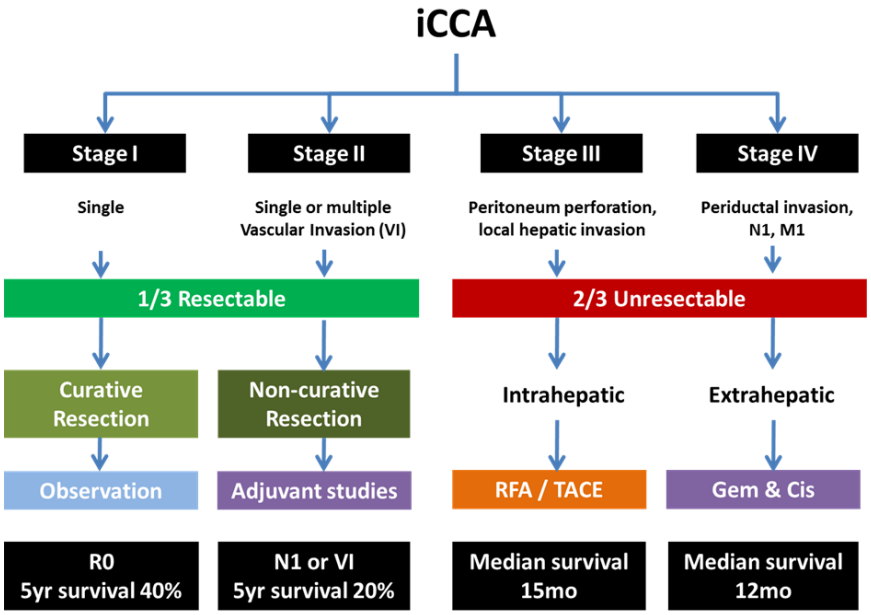
    NOTE: some tumours demonstrate a mixed pathology of HCC and CCA

Management

- One-third of patients will be resectable
  - With curative resection, 5 year survival of 40% can be achieved but this falls to only 20% if metastatic lymph nodes or vascular invasion are found at surgery

    NOTE: These iCCA patients are not candidates for liver transplant due to the high risk of recurrence and poor outcomes

- Two-thirds are unresectable
  - If intra-hepatic disease, RFA or TACE *[see Chapter 13.1]* can be offered but outcomes are worse than with HCC
  - If extra-hepatic disease, chemotherapy with gemcitabine and cisplatin can be offered but median survival is typically < 1 year



Adapted from Bridgewater J, et al. ILCA guidelines. J Hepatol 2014; 60(6):1268-89.

Abbreviations

AFP – alpha-fetoprotein

BCLC – Barcelona Clinic Liver Cancer

CA19-9 – carbohydrate antigen 19-9

CEA – carcinoembryonic antigen

Cis – cisplatin

CP – Child Pugh

DEB-TACE – transarterial chemoembolization with drug-eluting beads

ECOG – Eastern Cooperative Oncology Group

Gem – gemcitabine

H-DN – high-grade dysplastic nodule

HVPG – hepatic venous pressure gradient

IWP – international working party

L-DN – low-grade dysplastic nodule

M – metastasis

MD-HCC – moderately differentiated hepatocellular carcinoma

MDCT – multi-detection computerized tomography

N – lymph nodes

PDGF – platelet derived growth factor

PEI – percutaneous ethanol injection

PS – performance status

PVI – portal vein invasion

RCTs – randomized clinical trials

RFA – radiofrequency ablation

SBRT – stereotactic body radiation therapy

TARE – transarterial radioembolization

TTV – total tumour volume

VEGF – vascular endothelial growth factor

WD-HCC – well-differentiated hepatocellular carcinoma

Figure Citations

HCC Incidence. Source: World Health Organization. GLOBOCAN. Retrieved July 20,2017 from http://globocan.iarc.fr/Pages/Map.aspx

HCC Radiologic Diagnosis. Adapted from **Burak KW**. Chapter 23: Neoplasms of the Liver. In: First Principles of Gastroenterology and Hepatology. 2012; 463-473.

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iCCA Incidence, iCCA Treatment Algorithm. Adapted from Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; 60(6): 1268-89.

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