Hepatocellular Carcinoma HCC
Updated November 2015 by: Dr. Mohammed Alghamdi (Medical Oncology Fellow, University of Calgary), April 2017 by Dr. Jenny Ko (Medical Oncologist, Abbotsford Centre, BC Cancer Agency)

Staff Reviewers: Dr. Yoo-Joung Ko (Medical Oncologist, Sunnybrook Odette Cancer Centre, University of Toronto), Dr. Vincent Tam (Medical Oncologist, Tom Baker Cancer Centre, University of Calgary)

DISCLAIMER: The following are study notes compiled by the above medical oncology fellow and reviewed by staff medical oncologists. They reflect what we feel is relevant knowledge for graduating medical oncology residents preparing for their final examination. The information has not been surveyed or ratified by the Royal College.

A) PUBLIC HEALTH

EPIDEMIOLOGY
- **Incidence**: 18th most common cancer in Canadians (14th among men, 18th among women) (Canadian Cancer Statistics 2015)
  - 4.4 cases per 100,000 Canadians
  - 6th most common cancer worldwide (5th in men, 9th in women)
  - Highest-incidence regions: Sub-Saharan Africa, China, Hong Kong, Taiwan
  - Rising incidence in North America due to increasing rates of HCV infection and NASH leading to higher incidence of liver cirrhosis
- **Mortality**: 17th most common cause of cancer death in Canadians (12th among men, 18th among women) (Canadian Cancer Statistics 2015)
  - 2nd most common cause of cancer death worldwide

RISK FACTORS
- Liver cirrhosis
- Infections: chronic hepatitis B virus, chronic hepatitis C virus
- Alcoholic liver disease (Most common cause in North America)
- Metabolic liver disease (i.e. non-alcoholic steatohepatitis, hemochromatosis, Wilson’s disease, alpha1-antitrypsin deficiency)
- Autoimmune disease (i.e. autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis)
- Environmental toxins (i.e. aflatoxin, blue-green algae toxin, Betel nut chewing)

SCREENING
- Guidelines recommend screening for HCC in all cirrhotic patients and HBV carriers with **ultrasounds every 6 months**
  - Role of AFP in screening is controversial, but generally not recommended as a screening test

B) PRESENTATION & DIAGNOSIS

SYMPTOMS & SIGNS
- Most of the patients with HCC have underlying liver cirrhosis and hepatomas are identified on routine ultrasound screening of asymptomatic patients
- Symptoms depend on the location of the tumor, size and distant metastasis
- Symptoms can include: right upper quadrant abdominal pain, right shoulder pain, fatigue, anorexia, weight loss and unexplained fever are the most common symptoms.
INVESTIGATIONS
- Laboratory: (CBC, Chemistry, liver enzymes)
- Tumor marker: AFP
- Diagnostic Imaging:
  - Multi-phase liver CT (triphasic or quadraphasic) showing hypervascularity in the arterial phase and venous washout
  - MRI abdomen
  - Contrast-enhanced ultrasound
  - CT chest and abdomen to rule out metastases
  - Bone scan to rule out bone metastases
- Common sites of Metastases: lung, intra-abdominal lymph nodes, bone
- Diagnostic Procedures:
  - clinical diagnosis can be made (i.e. biopsy not necessary) in patients with liver cirrhosis if there is a nodule ≥1 cm + imaging shows hypervascularity in arterial phase with venous washout (American Association for the Study of Liver Disease Algorithm (AASLD), see below)
  - biopsy should be considered if a clinical diagnosis of HCC cannot be made or if required for clinical trial participation
  - large solitary lesions may be excised by hepatobiliary surgeon without need for biopsy
  - risk of seeding the needle tract estimated at 3%

AASLD Approach to Diagnosis of HCC in a Cirrhotic Liver

![AASLD Algorithm](image)

PATHOLOGY & MOLECULAR BIOLOGY
- Common Histology:
  - Hepatocellular carcinoma is the most common pathology
  - Fibrolamellar carcinoma is a variant of HCC which occurs more in young people, not associated with elevation of AFP and has a favorable prognosis
## STAGING

### - TNM

<table>
<thead>
<tr>
<th>TUMOUR</th>
<th>Stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>0</td>
<td>T1a, N0, M0</td>
</tr>
<tr>
<td>T0</td>
<td>I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>T1</td>
<td>II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>T2</td>
<td>IIIa</td>
<td>T3a, N0, M0</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIb</td>
<td>T3b, N0, M0</td>
</tr>
<tr>
<td>T3b</td>
<td>IVa</td>
<td>T4, N0, M0</td>
</tr>
<tr>
<td>T4a</td>
<td>IVB</td>
<td>T1/2/3/4, N0, M0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NODE S</th>
<th>Stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>0</td>
<td>T1a, N0, M0</td>
</tr>
<tr>
<td>N0</td>
<td>I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>N1</td>
<td>II</td>
<td>T2, N0, M0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>METASTASIS</th>
<th>Stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>0</td>
<td>T1a, N0, M0</td>
</tr>
<tr>
<td>M1</td>
<td>I</td>
<td>T1, N0, M0</td>
</tr>
</tbody>
</table>

### Barcelona Liver Clinic (BCLC) Staging System

<table>
<thead>
<tr>
<th>BCLC Stage</th>
<th>Tumour Stage</th>
<th>Child-Pugh Class</th>
<th>ECOG PS</th>
<th>Therapy options recommended by Sherman et al. 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early (0)</td>
<td>Single ≤ 2cm</td>
<td>A</td>
<td>0</td>
<td>Resection or Transplantation or RFA</td>
</tr>
<tr>
<td>Early (A)</td>
<td>Single ≤ 5cm</td>
<td>A or B</td>
<td>0</td>
<td>TACE</td>
</tr>
<tr>
<td>Intermediate (B)</td>
<td>Multinodular</td>
<td>A or B</td>
<td>0</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Advanced (C)</td>
<td>PVI, N1, M1</td>
<td>A or B</td>
<td>1-2</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>End-stage (D)**</td>
<td>Any</td>
<td>C</td>
<td>&gt;2</td>
<td>Symptomatic treatment</td>
</tr>
</tbody>
</table>
C) TREATMENT

Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines
(from the Alberta Health Services Clinical Practice Guideline: Hepatocellular Carcinoma)

Hepatocellular Carcinoma

Very Early Stage 0
Single tumour ≤2 cm

Early Stage A
Single tumour >2 cm or up to 3 tumours all ≤3 cm

Intermediate Stage B
> Milan criteria

Advance Stage C
PVI, N1, M1

Terminal Stage D

Child-Pugh A

Portal HT and/or bilirubin? Yes

LT candidate?

Yes

LT

No

Resection

Child-Pugh B

Child-Pugh C

Child-Pugh B ≤-9, C

Child-Pugh A, B ≤7

Child-Pugh A*

Child-Pugh B, C

ECOG PS

ECOG PS

0-1

≥2

0-2

> 2

PVT?

No

Yes

TARE TACE TARE

Sorafenib

Best Supportive Care

SBRT: SBRT can be considered when alternative therapies such as ablation/embolization techniques have failed or contraindicated, or for the palliation of symptoms.

Abbreviations / Notes: Milan criteria = single HCC ≤5cm or 3 HCC largest ≤3cm; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = metastasis; portal HT = portal hypertension (splenomegaly, esophageal varices, ascites, platelets < 100 or hepatic venous pressure gradient >10 mmHg); LT candidate = liver transplant candidate = total tumour volume <115mm³ AND alphafetoprotein <400ng/mL, age <70 (if age 65-69 no major comorbidities), good social support and appropriate abstinence and rehabilitation if addiction issues; ECOG PS= Eastern Cooperative Oncology Group performance status; PVT = portal vein thrombosis (bland); RFA = radiofrequency ablation; LT = liver transplantation; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT = stereotactic body radiotherapy.

* Consider enrolment of patients with Child-Pugh A, B ≤7 in a clinical trial.
**LOCALIZED / ADJUVANT**

- **Bottom Line General Approach:** Ideally managed by a multi-disciplinary team including hepatobiliary surgeons, hepatologists, radiologists and radiation oncologists since the treatment options include: surgical resection, liver transplant, RFA, TARE, TACE as per above figure

- **TACE (Transarterial chemoembolization):**
  - 80% of blood supply to tumors provided by hepatic artery, only supplies 25% of blood to liver
  - Ligation or embolization of the hepatic artery can result in tumor responses
  - Potentially even more efficacious when embolization combined with chemotherapy (e.g. doxorubicin, cisplatin, epirubicin)
  - Mainly used for large unresectable HCCs or multifocal HCCs not amenable to local treatments
  - Contraindicated in patients with: portal vein thrombosis/obstruction, encephalopathy, biliary obstruction, Childs-Pugh C liver cirrhosis
  - **Meta-analysis #1** (Llovet JM & Bruix JSO, Hepatology. 2003;37(2):429) compared arterial embolization with control (conservative management or suboptimal therapy) and showed a statistically significant improvement in 2-year survival with arterial embolization (OR = 0.53, 95% CI 0.32-0.89) but only for TACE and not bland embolization alone
  - **Meta-analysis #2** (Cardiovasc Intervent Radiol. 2007;30(1):6.) showed:
    - Significant survival benefit with TACE vs no treatment (OR for death = 0.705, 95% CI 0.50-0.99)
    - No survival advantage to TACE vs bland embolization (TAE)
    - No clearly superior chemotherapy agent
    - RR = 40%
    - Median survival = 18 months
    - Toxicities: acute liver failure, acute renal failure, encephalopathy, UGIB, hepatic abscess
    - Mortality = 2.4% mainly from acute liver failure
  - **Meta-analysis #3 (2012 Cochrane meta-analysis)** failed to find a survival benefit from either TACE or bland embolization (hazard ratio [HR] for death 0.81, 95% CI 0.64-1.02) overall, but after excluding 4 trials of arterial embolization undergoing resection of localized HCC (i.e. limiting the analysis to TACE for advanced HCC), there was a trend toward better survival, but it was not statistically significant (HR for death = 0.65, 95% CI 0.40-1.05)

- **Adjuvant Sorafenib:** STORM Trial compared adjuvant sorafenib to placebo after surgical resection or local ablation and found no recurrence-free survival benefit (Bruix J et al, Lancet Oncol. 2015;16(13):1344-54)

---

**ADVANCED / METASTATIC**

- **Bottom Line General Approach:**
  - First-line treatment: sorafenib or a clinical trial
  - Second-line treatments: regorafenib or a clinical trial
  - REACH: phase 3 trial with ramucirumab vs. placebo 2nd line (CP stage C or stage B with disease not amenable to locoregional therapy) – no OS benefit
  - CALGB 80802: phase 3 trial with doxorubicin + sorafenib vs sorafenib: higher toxicity and did not improve PFS or OS
  - CheckMate 040: phase I/II trial with biomarker unselected HCC patients – ORR 18.6%
### SHARP Trial
**Sorafenib in Advanced Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>• Sorafenib 400mg po BID vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action of Experimental Drug</td>
<td>Small molecule that inhibits tumour cell proliferation, tumour angiogenesis and increases the rate of apoptosis by inhibiting multiple tyrosine kinase including Raf-1, B-Raf, VEGFRs 1,2,3 and PDGFR-B.</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Overall survival and the time to symptomatic progression.</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>• Advanced stage HCC, no prior systemic therapy, ECOG 2 or less, Child-Pugh liver function class A</td>
</tr>
<tr>
<td>Size (N)</td>
<td>• 602 patients</td>
</tr>
</tbody>
</table>
| Results | Median Survival = 10.7 months vs. 7.9 months, P<0.001  
Time to Symptomatic Progression = 4.1 months vs. 4.9 months, P=0.77  
Time to Radiologic Progression = 5.5 months 2.8 months (P<0.001)  
Response Rate: 2% vs. 1% |
| Toxicity | Diarrhea, weight loss and hand–foot skin reaction were more frequent in the sorafenib group. |
| Conclusion | In patients with advanced hepatocellular carcinoma, median survival and time to radiologic progression were approximately 3 months longer for patients treated with sorafenib compared to placebo |

### Asia-Pacific Trial
**Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>• Sorafenib 400mg po BID vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action of Experimental Drug</td>
<td>Small molecule that inhibits tumour cell proliferation, tumour angiogenesis and increases the rate of apoptosis by inhibiting multiple tyrosine kinase including Raf-1, B-Raf, VEGFRs 1,2,3 and PDGFR-B.</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>No predefined primary endpoint; OS, TTP, time to symptomatic progression, disease control rate, and safety were assessed</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>• Advanced stage HCC, no prior systemic therapy, ECOG 2 or less, Child-Pugh liver function class A, 18 years or older</td>
</tr>
<tr>
<td>Size (N)</td>
<td>• 271 patients</td>
</tr>
</tbody>
</table>
| Results | Median Survival = 6.2 months vs. 4.2 months, P<0.014  
Time to Progression = 2.8 months vs. 1.4 months, P=0.0005  
Time to Symptomatic Progression = 3.5 months vs. 3.4 months, P=0.50  
Response Rate = 3.3% vs. 1.3% |
| Toxicity | Diarrhea, hand–foot skin reaction, HTN more frequent with sorafenib |
| Conclusion | HCC patients randomized to treatment with sorafenib had significantly longer overall survival than did those who received placebo |

### Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.
*Lancet*. 2017 Jan
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Best supportive care plus oral regorafenib 160 mg or placebo once daily during weeks 1-3 of each 4-week cycle.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>OS</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Adults with HCC who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function</td>
</tr>
<tr>
<td>Size (N)</td>
<td>N=573</td>
</tr>
<tr>
<td>Results</td>
<td>Regorafenib improved overall survival with a hazard ratio of 0·63 (95% CI 0·50-0·79; one-sided p&lt;0·0001); median survival was 10·6 months (95% CI 9·1-12·1) for regorafenib versus 7·8 months (6·3-8·8) for placebo.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Adverse events were reported in all regorafenib recipients (374 [100%] of 374) and 179 (93%) of 193 placebo recipients. The most common clinically relevant grade 3 or 4 treatment-emergent events were hypertension (57 patients [15%] in the regorafenib group vs nine patients [5%] in the placebo group), hand-foot skin reaction (47 patients [13%] vs one [1%]), fatigue (34 patients [9%] vs nine patients [5%]), and diarrhoea (12 patients [3%] vs no patients). Of the 88 deaths (grade 5 adverse events) reported during the study (50 patients [13%] assigned to regorafenib and 38 [20%] assigned to placebo), seven (2%) were considered by the investigator to be related to study drug in the regorafenib group and two (1%) in the placebo group, including two patients (1%) with hepatic failure in the placebo group.</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Regorafenib is the only systemic treatment shown to provide survival benefit in HCC patients progressing on sorafenib treatment.</td>
</tr>
</tbody>
</table>

- **Prognosis:** Median survival without treatment about 4-8 months, with sorafenib treatment 6-11 months

**D) REFERENCES**
- Alberta Health Services cancer guide line.
- Canadian cancer statistic 2015
- UpToDate 2015
- AASLD Practice Guideline, Management of Hepatocellular Carcinoma: An Update. Bruix, J, Sherman, M.