HEPATOCELLULAR CARCINOMA

Effective Date: December 2017
The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial GI Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GI Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
BACKGROUND

Cirrhosis represents a diffuse liver disease characterized by structurally abnormal nodules of liver cells surrounded by fibrosis. It results from chronic liver injury and regeneration secondary to chronic viral hepatitis, alcoholic liver disease, metabolic liver diseases (e.g.: hemochromatosis, Wilson’s disease, \( \alpha_1 \)-antitrypsin deficiency, non-alcoholic steatohepatitis), and autoimmune diseases (e.g.: autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis). Cirrhosis is associated with an annual incidence of hepatocellular carcinoma of 3 to 5 percent.

Hepatocarcinogenesis represents a multi-step process in which both genetic abnormalities and epigenetic alterations encourage the malignant transformation of hepatocytes. Hepatocellular carcinomas are associated with up-regulated signal transduction through multiple pathways (e.g.: mitogen-activated protein kinase, vascular endothelial growth factor receptor).

Prognosis depends upon the extent of hepatic replacement by the tumour, the alpha-fetoprotein (AFP) level, the patient’s performance status (see Appendix B), the tumour’s histologic subtype (e.g.: fibrolamellar variant), and the degree of liver dysfunction (as assessed by the Child-Pugh classification system, see Appendix C).

GUIDELINE QUESTIONS

- What are the goals of therapy and recommendations for the treatment of adult patients with:
  - very early stage hepatocellular carcinoma?
  - early stage hepatocellular carcinoma?
  - intermediate stage hepatocellular carcinoma?
  - advanced stage hepatocellular carcinoma?
  - terminal stage hepatocellular carcinoma?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists, gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in August 2009. This guideline was revised in March 2010, June 2011, October 2013, March 2014, June 2015 and Dec 2017.

SEARCH STRATEGY

This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related
information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team’s interpretation of the data. The 2015 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2014 Annual Gastrointestinal Tumour Team Meeting.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with hepatocellular carcinoma (HCC). Different principles may apply to pediatric patients.

RECOMMENDATIONS AND DISCUSSION

Suggested Diagnostic Work-up

To define the intra-hepatic extent of disease and to exclude the presence of extra-hepatic metastases and/or tumour thrombi within the hepatic vein, inferior vena cava, or portal vein, a CT scan of the abdomen (in both hepatic arterial and portal venous phases) and/or a breath-hold dynamic contrast enhanced MR liver are recommended.

The American Association for the Study of Liver Disease (AASLD) has established an algorithm for the evaluation of liver nodules in a cirrhotic liver; this algorithm has been prospectively validated. For nodules over 2 cm in diameter, the diagnosis of hepatocellular carcinoma can often be made if either an imaging modality identifies arterial hyper-vascularity or the alpha-fetoprotein level exceeds 200 ng/mL; that is, a biopsy may not be necessary to establish the diagnosis. In fact, there is a 10.6 percent risk of a false negative and a 2.3 percent chance of tumour seeding with a liver biopsy. For nodules between 1 and 2 cm, the diagnosis can often be made if two imaging modalities identify arterial hypervascularity and venous phase washout. Atypical findings or absence of cirrhosis warrant a biopsy. For nodules under 1 cm, repetition of the imaging studies (usually with ultrasound) in three months is recommended.

More recently, the AASLD diagnostic algorithm has been simplified and has removed the role of AFP in the diagnosis of HCC in a cirrhotic liver for lesions greater than 1 cm in size (Figure 1).

HCCs can metastasize to lung and bone. A chest x-ray or CT scan of the thorax (in addition to the CT scan of the abdomen) and a bone scan may help to identify other extra-hepatic disease.

Blood work assesses the functional status of the liver and helps to establish the Child-Pugh score (see Appendix C for details).

Goals and Recommendations

To define and provide optimal care to a patient with HCC, a multidisciplinary team (MDT) is required. It should be composed of hepatobiliary surgeons, diagnostic and interventional radiologists, hepatologists, gastroenterologists, and oncologists. Consideration is given to patient factors (e.g.: functional status, comorbidities, liver function) and tumour factors (e.g.: size, number, location, vascular invasion).

The Barcelona Clinic Liver Cancer (BCLC) staging system (Table 1) provides a system to define the care for patients with HCC. It links the TNM staging system (see Appendix A), the patient’s ECOG performance status (see Appendix B), and the patient’s liver function (see Appendix C) to treatment
options. An algorithm for management of HCC according to the updated AHS clinical practice guideline recommendations is provided (Figure 2).

Consider treatment on a clinical trial, if available.

**Figure 1.** Diagnosis of HCC in a Cirrhotic Liver.\(^6\)
Table 1. Barcelona Clinic Liver Cancer Staging System.\textsuperscript{7*}

<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\textsuperscript{7}</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 or up to three all ≤ 3cm</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</td>
<td>1-2</td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td>End-stage (D)\textsuperscript{**}</td>
<td>Any</td>
<td>C</td>
<td>&gt;2</td>
<td>Symptomatic treatment</td>
</tr>
</tbody>
</table>

\textsuperscript{7*}This table is adapted from Sherman et al. 2011\textsuperscript{7} Please see Figure 2 for Alberta specific recommendations for the management of HCC

\textsuperscript{**}Patients who are PVI, N1, M1 and Child-Pugh B or C may be treated as end-stage.

BCLC = Barcelona Clinic Liver Cancer; PS = performance status; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = distant metastasis; PS = Performance Status; RFA = radiofrequency ablation; TACE = transarterial chemoembolization
Figure 2. Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines (adapted from the Alberta\textsuperscript{8} and Canadian\textsuperscript{7} HCC algorithms).

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 >10mmHg); LT candidate = liver transplant candidate = total tumour volume <115mm\textsuperscript{3} 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 enrollment of patients with Child-Pugh A, B 7 in a clinical trial.
**Table 2. Definitions, Goals, and Recommendations for Management of Hepatocellular Carcinoma.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definitions, Goals, and Recommendations:</th>
</tr>
</thead>
</table>
| **Very Early Stage Hepatocellular Carcinoma** | **Patient Requirements:** Good performance status (ECOG 0). Well-compensated liver function (Child-Pugh class A).  
**Tumour Requirements:** Solitary tumour (< 2 cm) confined to one lobe of the liver. Absence of vascular invasion and extra-hepatic disease. Complete removal of the tumour with a margin of ≥ 1 cm anticipated.  
**Goals:** To render patient free of disease and to delay or prevent recurrence.  
**Recommendation:** Resection. | **Resection:**  
In carefully selected patients, five-year survivals of 50 to 70% are anticipated.  
Comparative genomic hybridization reveals that 60 to 70% of recurrences are intra-hepatic metastases and that 30 to 40% are de novo tumour development.  
Abnormal bilirubin and portal hypertension (as suggested by thrombocytopenia with platelet count under 100, varices, ascites, and/or splenomegaly) predict for failure to benefit from resection.  
If extra-hepatic disease is confirmed at laparotomy, resection is not pursued.  
Intra-operative ultrasound and bi-manual palpation assess for other intra-hepatic lesions. Intra-operative or subsequent radiofrequency ablation or percutaneous ethanol injection can be considered for multicentric disease.  
No clear benefit has been established for adjuvant therapy post-resection. In fact, adjuvant chemotherapy may adversely affect the outcome, especially in cirrhotic patients. Sorafenib was of no benefit as adjuvant therapy following curative intent resection or radiofrequency ablation (STORM study).  
In patients who are not candidates for surgical resection, radiofrequency ablation (see below) can offer a 97% complete response for tumour ≤ 2 cm with long-term survival similar to what has been reported in patients who have undergone resection.  
Three randomized controlled trials comparing surgical resection to RFA have been performed in China. Although the studies had methodological flaws (cross-over between groups), similar outcomes were reported in two studies whereas one study demonstrated improved recurrence-free and overall survival in the surgical resection group.  
**Follow-Up:** To identify recurrence, obtain a contrast enhanced CT scan, MR, or ultrasound of the abdomen every three months for two years and then every six months thereafter. Obtain an AFP every three months for two years and then every six months thereafter. |
| **Early Stage Hepatocellular Carcinoma** | **Patient Requirements:** Good performance status (ECOG 0). Well-compensated liver function (Child-Pugh class A).  
**Tumour Requirements:** Solitary tumour confined to one lobe of liver or three nodules (all ≤ 3 cm)  
Absence of vascular invasion and extra-hepatic disease. Complete removal of the tumour(s) with a margin of ≥ 1 cm anticipated.  
**Goals:**  
**Recommendations:** Resection (see above), liver transplantation (see below), or ablation (see below).  
**Liver Transplantation:**  
Removes the cancer and corrects the underlying “field defect” (cirrhosis) but subjects the patient to the potential complications of long-term immunosuppression.  
Offers a five-year disease-free survival of up to 70% and a short-term mortality of 5 to 10%.  
In Alberta, transplantation is not recommended if the total tumour volume (TTV) exceeds 115 cm³, the alpha-fetoprotein exceeds 400 ng/mL, vascular invasion and/or extra-hepatic disease exist, significant co-morbidities exist, or the patient fails to abstain from alcohol for at least six months. |
Patients may be considered for liver transplantation after being “down-staged” if their initial total tumour volume was under 250 cm$^3$ and both the total tumour volume and the AFP remain under 115 cm$^3$ and 400 ng/mL, respectively, for more than six months.\textsuperscript{20,21}

### Radiofrequency Ablation (RFA) or Percutaneous Ethanol Injection (PEI):
- Provides tumour control pending transplantation or as an adjunct or alternative to resection.
- Recent series of radiofrequency ablation report local recurrence rates under 5% and five-year survivals equal to resection. Radiofrequency ablation requires fewer sessions to ablate tumours and results in improved survival when compared to percutaneous ethanol injection.\textsuperscript{22}
- Survival rates with radiofrequency ablation may be similar to surgical resection;\textsuperscript{17} however, two-year recurrence rates are higher following percutaneous ethanol injection and radiofrequency ablation than with resection.\textsuperscript{23}
- Best outcomes are achieved from radiofrequency ablation when tumours are centrally located, measure under 3 cm, and are distant from “heat sinks” (blood vessels).\textsuperscript{10} Consider percutaneous ethanol injection or transarterial chemo-embolization (TACE) when tumours are in a subcapsular location, exceed 4 cm, or are located adjacent to blood vessels.
- Hepatocellular carcinomas are considered “treated” only if the imaging study demonstrates complete tumour necrosis (without contrast enhancement to suggest residual disease).

### Intermediate Stage Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Patient Requirements</th>
<th>Tumour Requirements</th>
<th>Goals</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good performance status (ECOG 0-1).</td>
<td>Multinodular disease.</td>
<td>To maintain or to improve the patient’s quality of life (to control or to delay the onset of tumour-related symptoms, possibly while awaiting transplant).</td>
<td>Transarterial chemo-embolization\textsuperscript{24-28} or transarterial radioembolization.\textsuperscript{29-32}</td>
</tr>
<tr>
<td>Well-compensated liver function (Child-Pugh class A) and only select patients with impaired liver function (Child-Pugh class B 7).</td>
<td>Absence of extra-hepatic disease.</td>
<td>To prolong life, if possible.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patency of the main portal vein (as assessed by ultrasound Doppler or MR angiography) for TACE.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate renal function.</td>
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<td></td>
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</tbody>
</table>

### Transarterial Chemo-Embolization (TACE):\textsuperscript{33,34}
- Blood supply to hepatocellular carcinomas is preferentially derived from the hepatic artery rather than the portal vein.
- Involves placement of an intravascular catheter into the hepatic artery (inserted percutaneously in the femoral artery and advanced through the abdominal aorta and celiac trunk). Injection of chemotherapy (with or without the oily contrast agent, Lipiodol) followed by embolic agents (e.g.: gelatin-sponge particles, Embosphere\textsuperscript{®}) occludes the relevant branch of the hepatic artery and localizes the chemotherapy. Meta-analyses of randomized controlled trials demonstrate a survival benefit of TACE.\textsuperscript{33,34} Drug-eluting beads (DEBs) decrease the systemic exposure to doxorubicin.\textsuperscript{35} Although DEBs have not been shown to be superior to conventional TACE, they offer a more standardized technique and are better tolerated with fewer complications.\textsuperscript{27} Recent cohort studies are demonstrating median survival of 4 years after TACE with DEBs in carefully selected patients.\textsuperscript{28}
- If Doxorubicin is considered, assess the left ventricular ejection fraction with a MUGA scan or echocardiogram prior to the procedure. It is not clear if MUGA or ECHO is still required before TACE with DEBs.

### Transarterial Radioembolization (TARE):\textsuperscript{36}
- TARE or selective internal radiotherapy (SIRT) uses microsphere loaded with yttrium-90 (Y$^{90}$) to deliver radiation directly into the tumour via the hepatic artery. Unlike TACE it is
done as an outpatient. Prior to the TARE, the patient requires a staging angiogram to calculate the liver-to-lung shunt fraction in Nuclear Medicine using technicium-99 macro-aggregated albumin (Tc99 MAA). At the same time selective embolization of the gastroduodenal arteries is carried out to prevent delivery of radiation to the stomach and duodenum. The procedure may be repeated depending upon response.

- There are no direct comparisons of TARE with TACE. However, large cohort studies from Europe29 and the USA30 have shown similar survival to TACE in BCLC stage B patients.
- TARE, unlike TACE, can be performed safely in patients with portal vein thrombosis, as the microspheres used in TARE are smaller and less embolic.29,30
- TARE may be considered for patients who have progressive disease after TACE, who cannot tolerate doxorubicin or who are likely to fail TACE (large HCC).
- TARE may also be more effective than TACE in bridging or down-staging patients to liver transplantation.31,33
- Outcomes following TARE are best in patients with preserved liver function (Child-Pugh score <8 or MELD score <13).32 Patients should be selected for TARE at MDT meetings.
- As there remains uncertainty about TARE efficacy compared to TACE (intermediate stage) or sorafenib (advanced stage), clinical trials are encouraged.

### Advanced Stage Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Patient Requirements</th>
<th>Tumour Requirements</th>
<th>Goals</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good performance status (ECOG 0, 1, or 2).</td>
<td>Disease ineligible for, or that progressed after, surgical or locoregional therapy.</td>
<td>To maintain or to improve the patient’s quality of life (to control or to delay the onset of tumour-related symptoms).</td>
<td>First-line treatment: Sorafenib or participation in a clinical trial,36 if available.</td>
</tr>
<tr>
<td>Well-compensated liver function (Child-Pugh class A).</td>
<td></td>
<td>To prolong life, if possible.</td>
<td>Second-line treatment: participation in a clinical trial,36 if available.</td>
</tr>
</tbody>
</table>

**Sorafenib 400 mg po BID:**

- Represents an orally active inhibitor of multiple cell surface tyrosine kinases (e.g.: VEGFR, PDGFR-β, c-kit, FLT3, RET) as well as downstream intracellular kinases (e.g.: Raf) involved in angiogenesis and tumour progression.
- Delays progression and improves overall survival when compared to placebo in two randomized, double blind, placebo-controlled, phase III trials:

<table>
<thead>
<tr>
<th>End-Point</th>
<th>SHARP Trial37</th>
<th>Asia-Pacific Trial38</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td>Median Survival</td>
<td>10.7 months</td>
<td>7.9 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.69 (CI 95% 0.55-0.87)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Time to Progression (Radiologic)</td>
<td>5.5 months</td>
<td>2.8 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.58 (CI 95% 0.45-0.74)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
• Hypothyroidism develops in 18% of patients within two to four months of starting Sorafenib. Obtain a baseline TSH and then monitor levels every six weeks.33
• Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, p = 0.015).34

**Stereotactic Body Radiotherapy (SBRT)**

• There is growing experience with providing ionizing radiotherapy to HCC using very conformal dose distribution, with image guidance and motion management to provide high doses of radiation to the HCC while minimizing exposure to the adjacent liver or other tissues.39
• SBRT can provide good local control of HCC range (ranging from 43% to 100% at 1 year) which can depend on factors such as lesion size and number, and the delivered radiation dose. It has been used in patients with portal vein invasion 40 and to bridge patients to liver transplantation.41
• Patients should be discussed at multidisciplinary rounds. SBRT can be considered when alternative therapies such as ablation/embolization techniques have failed or are contraindicated.
• Patients can experience worsening of liver function with SBRT40 and tolerance to normal liver is the main dose limiting constraint. Most safety evidence is for patients with Child-Pugh class A disease. Evidence is more limited for Child-Pugh class B disease and in practice treatment dose is lowered to reduce the chance of treatment toxicities. Treatment of patients with Child-Pugh class C disease is not recommended as the safety of liver SBRT in this population has not been determined.
• Continued clinical trials in the use of liver SBRT are recommended. Studies evaluating SBRT in combination with sorafenib are currently underway. Enrollment of patients into clinical trials or investigational protocols should be encouraged.

<table>
<thead>
<tr>
<th>Terminal Stage Hepatocellular Carcinoma</th>
<th>Patient Requirements:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Poor performance status (ECOG &gt; 2).</td>
</tr>
<tr>
<td></td>
<td>• Decompensated liver function (Child-Pugh class C).</td>
</tr>
<tr>
<td>Goals:</td>
<td>To maintain or to improve the patient’s quality of life (to control tumour-related symptoms).</td>
</tr>
<tr>
<td>Recommendations:</td>
<td>• Best supportive care.</td>
</tr>
<tr>
<td></td>
<td>• Palliative chemotherapy may adversely affect outcome.42</td>
</tr>
</tbody>
</table>

**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Disease</td>
</tr>
<tr>
<td>AHS</td>
<td>Alberta Health Services</td>
</tr>
<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>BCLC</td>
<td>Barcelona Clinic Liver Cancer</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DEB</td>
<td>drug-eluting bead</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>MDT</td>
<td>multidisciplinary team</td>
</tr>
<tr>
<td>MR</td>
<td>magnetic resonance</td>
</tr>
<tr>
<td>MELD</td>
<td>Model for End-stage Liver Disease</td>
</tr>
<tr>
<td>PEI</td>
<td>percutaneous ethanol injection</td>
</tr>
</tbody>
</table>
DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

REFERENCES

   Level of Evidence: 1a
   Level of Evidence: 1a
   Level of Evidence: 2b
   Level of Evidence: 1b
   Level of Evidence: 3a
   Level of Evidence: 2a
   Level of Evidence: 1a, 2a, 3a
Level of Evidence: 1a, 2a, 3a
Level of Evidence: 3a
Level of Evidence: 2b
Level of Evidence: 2b
Level of Evidence: 3a
Level of Evidence: 1b
Level of Evidence: 2b
Level of Evidence: 1b
Level of Evidence: 5
Level of Evidence: 1b
Level of Evidence: 1b
Level of Evidence: 1b
Level of Evidence: 2c
Level of Evidence: 2c
Level of Evidence: 1a
Level of Evidence: 2c

Level of Evidence: 1a

Level of Evidence: 1a

Level of Evidence: 1a

Level of Evidence: 1b

Level of Evidence: 2b

Level of Evidence: 2b

Level of Evidence: 2b

Level of Evidence: 4

Level of Evidence: 4

Level of Evidence: 1a

Level of Evidence: 1a

Level of Evidence: 2b

Level of Evidence: 1a

Level of Evidence: 1b
Level of Evidence: 1b
Level of Evidence: 3a
Level of Evidence: 2b
Level of Evidence: 4
Level of Evidence: 1a

<table>
<thead>
<tr>
<th>Level</th>
<th>Description of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews of randomized controlled trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized controlled trials</td>
</tr>
<tr>
<td>1c</td>
<td>All or none randomized controlled trials</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or low quality randomized controlled trial</td>
</tr>
<tr>
<td>2c</td>
<td>Outcomes research</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour Description</th>
<th>Regional* Lymph Node Involvement</th>
<th>Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T&lt;sub&gt;1&lt;/sub&gt; Solitary tumour without vascular invasion</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; Absent</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage II</td>
<td>T&lt;sub&gt;2&lt;/sub&gt; Solitary tumour with vascular invasion or multiple tumours (all ≤ 5 cm)</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; Absent</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage III&lt;sub&gt;A&lt;/sub&gt;</td>
<td>T&lt;sub&gt;3a&lt;/sub&gt; Multiple tumours (with any &gt; 5 cm)</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; Absent</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage III&lt;sub&gt;B&lt;/sub&gt;</td>
<td>T&lt;sub&gt;3b&lt;/sub&gt; Tumour involves major branch of portal or hepatic veins</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; Absent</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage III&lt;sub&gt;C&lt;/sub&gt;</td>
<td>T&lt;sub&gt;4&lt;/sub&gt; Direct invasion of adjacent organ (other than gallbladder) or perforation of visceral peritoneum</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; Absent</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage IV&lt;sub&gt;A&lt;/sub&gt;</td>
<td>T&lt;sub&gt;any&lt;/sub&gt; As above</td>
<td>N&lt;sub&gt;1&lt;/sub&gt; Present</td>
<td>M&lt;sub&gt;0&lt;/sub&gt; Absent</td>
</tr>
<tr>
<td>Stage IV&lt;sub&gt;B&lt;/sub&gt;</td>
<td>T&lt;sub&gt;any&lt;/sub&gt; As above</td>
<td>N&lt;sub&gt;any&lt;/sub&gt; As above</td>
<td>M&lt;sub&gt;1&lt;/sub&gt; Present</td>
</tr>
</tbody>
</table>

*Note: Regional refers to lymph nodes located at the liver hilum (e.g.: hepatoduodenal ligament, hepatic, periportal), in the inferior phrenic location, or along the inferior vena cava, hepatic artery, or portal vein.
APPENDIX B: ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active and able to carry on without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care and/or confined to a bed or chair for more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.</td>
</tr>
</tbody>
</table>
APPENDIX C: Child-Pugh Classification System

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score 1 Point</th>
<th>Score 2 Points</th>
<th>Score 3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>Grade 0</td>
<td>Grade 1 or 2 (or suppressed with medications)</td>
<td>Grade 3 or 4 (or refractory)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Suppressed with medications</td>
<td>Refractory</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Under 34 µM</td>
<td>Between 34 at 50 µM</td>
<td>Over 50 µM</td>
</tr>
<tr>
<td>Albumin</td>
<td>Over 35 g/L</td>
<td>Between 28 and 35 g/L</td>
<td>Under 28 g/L</td>
</tr>
<tr>
<td>PT-INR</td>
<td>Under 1.7</td>
<td>Between 1.7 and 2.2</td>
<td>Over 2.2</td>
</tr>
</tbody>
</table>

**Encephalopathy:**
- Grade 0: Normal cognition
- Grade 1: Euphoria, fluctuation in level of consciousness, and slurred or disoriented speech
- Grade 2: Drowsiness, inappropriate behavior, and loss of sphincteric control
- Grade 3: Marked confusion, stupor, and incoherent speech
- Grade 4: Coma

Grade A: Total score of 5 to 6 — Considered “well-compensated liver function”
Grade B: Total score of 7 to 9 — Considered “significant functional impairment”
Grade C: Total score of 10 to 15 — Considered “decompensated liver function”