Guideline Resource Unit
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Hepatocellular Carcinoma

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Cancer Care Alberta

Clinical Practice Guideline GI-007 – Version 8
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Background

Cirrhosis represents a diffuse liver disease characterized by structurally abnormal nodules of liver cells surrounded by fibrosis.[1] 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, α_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 α-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?

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 2021 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2020 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

At Risk Population:

The American Association for the Study of Liver Disease (AASLD) promotes routine HCC surveillance for all adult patients with Child-Pugh A or B cirrhosis.[2] Screening and surveillance using liver ultrasound, with or without α-fetoprotein (AFP), is recommended every six months. Patients with Child-Pugh C cirrhosis are not recommended for surveillance due to low anticipated survival unless these patients are on a liver transplant waiting list (see Appendix C for details on Child-Pugh score). Patients with hepatitis B are also considered at risk; screening is recommended starting at age 40 for Asian males, age 50 for Asian females and age 20 for those of African descent.[2] The American College of Radiology (ACR) has created the Ultrasound Liver Imaging Reporting and Data System (US LI-RADS) algorithm for interpretation and reporting of ultrasound exam results.[3] The US LI-RADS is composed of 3 observational categories and 3 visualization scores, which are summarized in Table 1. An AFP value that exceeds 20 ng/mL is considered positive, while anything lower is considered negative.[3]

Table 1: US LI-RADS for Surveillance[3, 4]

Observation categories		
Category	**Definition**	**Recommendation**
US-1 Negative	No observation, or only definitely benign observation(s)	6 month follow-up ultrasound
US-2 Subthreshold	Observation(s) < 10 mm in diameter, not definitely benign	Ultrasound follow-up at 3-6 months
US-3 Positive	Observation(s) ≥ 10 mm in diameter, not definitely benign, or new thrombus in vein	Multiphasic contrast-enhanced CT or MRI or Contrast enhanced US

Visualization scores		
Score	**Concept**	**Examples**
A. No or minimal limitations	Limitations unlikely to affect sensitivity	-Liver: homogeneous or minimally heterogeneous -Minimal beam attenuation or shadowing -Close to entire liver visualized
B. Moderate limitations	Small masses may be obscured	-Liver: moderately heterogeneous -Moderate beam attenuation or shadowing -Some regions of liver or diaphragm not visualized
C. Severe limitations	Significantly decreased sensitivity for focal liver lesions	-Liver: severely heterogeneous -Severe beam attenuation of shadowing -Most (> 50%) of liver and most (> 50%) of diaphragm not visualized

Noninvasive diagnosis with a multiphase CT scan or a multiphase MRI is recommended by the AASLD.[2] The results should be interpreted and reported through the CT/MRI Liver Imaging Reporting and Data System (CT/MRI LI-RADS) algorithm developed by the ACR. This algorithm allows definitive diagnosis of HCC in high risk patients without pathologic confirmation.[5] The CT/MRI LI-RADS outlines eight diagnostic categories summarized in Table 2. The key imaging features include size ≥ 1 cm, arterial phase hyperenhancement (APHE), and a combination of washout, threshold

growth and capsule appearance.[6] If these features are not present but HCC is suspected, then a liver biopsy should be considered. A biopsy should also be considered in patients with a liver mass that is atypical of HCC on contrast-enhanced imaging[2]. If high-grade dysplasia and HCC are not disguisable by routine histology alone, tumour markers glypican-3 (GPC3), heat-shock protein 70 (HSP70) and glutamine synthetase (GS) can be assessed.

Table 2: Summary of CT/ MRI LI-RADS categories[5]

Diagnostic Category	Conceptual Definition	CT/MRI Criteria
LR-NC: Noncategorizable	Observation cannot be categorized due to image omission or degradation	- One or more major feature cannot be assessed AND - As a direct result, possible categories range from unlikely cancer (LR-1 or LR-2) to likely cancer (LR-4, LR-5, LR-M)
LR-1: Definitely Benign	100% certainly that observation is nonmalignant	- LI-RADS does not provide criteria for most entities categorized LR-1 but example: a simple cyst, typical hemangiomas
LR-2: Probably Benign	High probability but not 100% certainty observation is non-malignant	Distinctive nodule: - size <20 mm - NO major features, LR-M features or ancillary features of malignancy -Example: T1 hyperintense nodules, T2 hypointense nodules, hepatobiliary phase hyperintense nodules
LR-3: Intermediate probability of malignancy	Nonmalignant & malignant entities each have moderate probability	**Nonrim arterial phase hyperenhancement AND:** - < 20 mm with no additional features **Arterial phase hypo- or isoenhancement AND:** - < 20 mm with ≤ 1 additional major features OR - ≥ 20 mm with no additional major features
LR-4: Probably HCC	High probability but not 100% certainty observation is HCC	**Nonrim arterial phase hyperenhancement AND:** - < 10 mm with ≥ 1 additional features OR - 10-19 mm with “capsule” and no other major features OR - ≥ 20 mm with no additional major feature **Arterial phase hypo- or isoenhancement AND:** - < 20 mm with ≥ 2 additional major features OR - ≥ 20 mm with ≥ 1 additional major features
LR-5: Definitely HCC	100% certainty observation is HCC	**Nonrim arterial phase hyperenhancement AND:** -10-19 mm with nonperipheral “washout” and no other majpr features OR - 10-19 mm with ≥ 50% size increases in ≤ 6 months and no other major features OR - ≥ 20 mm with ≥ 1 additional major feature
LR-TIV: Malignancy with tumour in vein	100% certainty there is malignancy with tumour in vein	Presence of definite enhancing soft tissue in vein, regardless of visualization of parenchymal mass
LR-M: Probably or definitely malignant, not HCC specific	High probability of 100% certainty observation is malignant but features are not HCC specific (does not exclude HCC, indicates chances of different neoplasm)	**Targetoid mass:** -Rim APHE -Peripheral washout appearance -Delayed central enhancement -Targetoid diffusion restriction -Targetoid TP or HBP signal intensity **Nontargetoid mass not meeting LR-5 criteria and without TIV, with ≥ 1 of the following:** -infiltrative appearance -marked diffusion restriction -necrosis or severe ischemia -Other feature suggesting non-HCC malignancy

Population Not at Increased Risk:

HCC diagnosis cannot be made on imaging results alone, even if washout and enhancement are present. Patients not at high risk for developing HCC require a biopsy.[6]

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, co-morbidities, liver function) and tumour factors (e.g. size, number, location, vascular invasion).

The Barcelona Clinic Liver Cancer (BCLC) staging system (Table 3) provides a system to define the care for patients with HCC.[7, 8] 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 1).

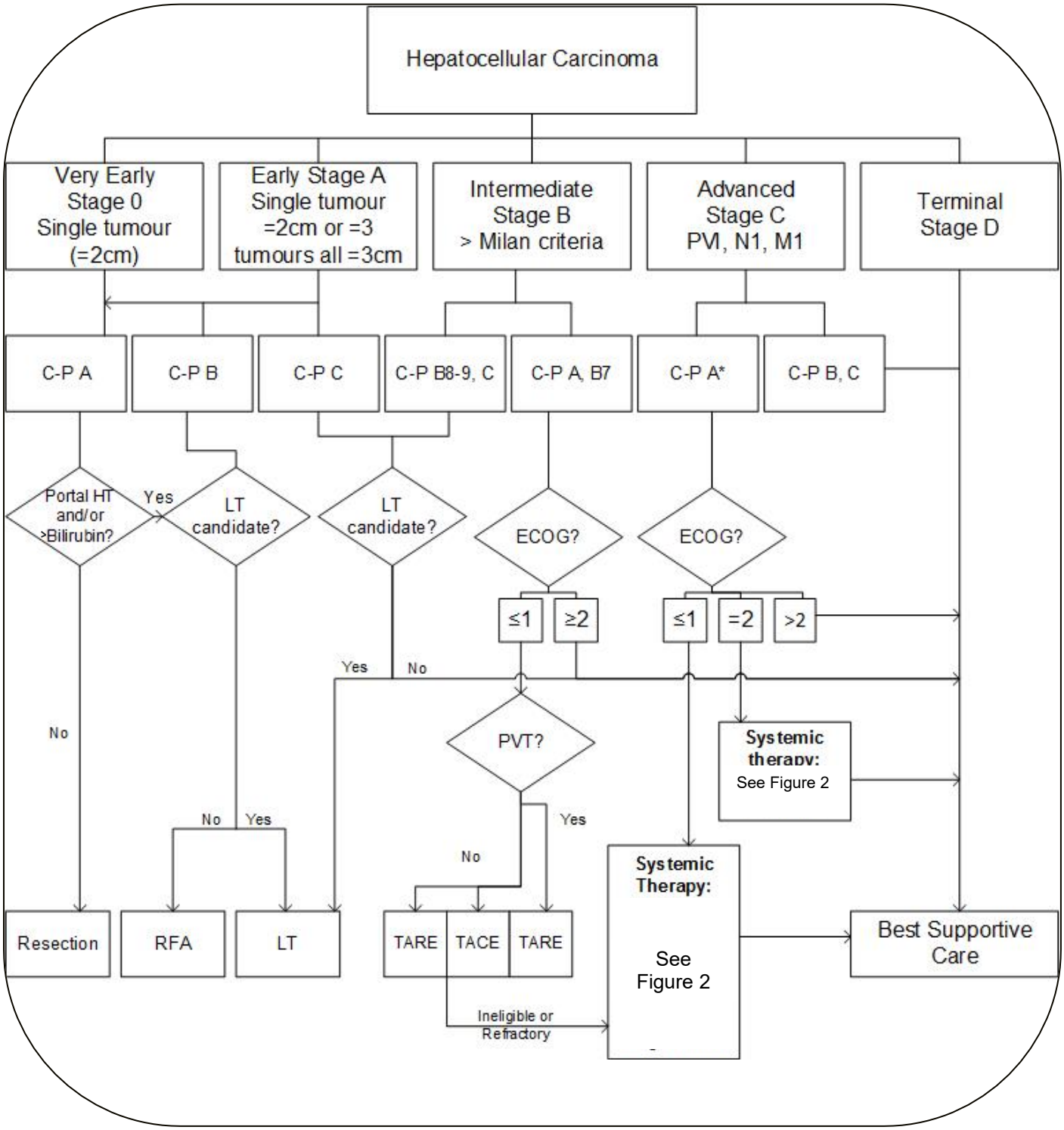
Consider treatment on a clinical trial, if available.

Table 3. Barcelona Clinic Liver Cancer Staging System.[8]*

BCLC Stage	Tumour Stage	Child-Pugh Class	ECOG PS	Therapy options recommended by Sherman et al. 2011[7]
Very early (0)	Single ≤ 2cm	A	0	Resection or Transplantation or RFA
Early (A)	Single ≤ 5cm Or up to three all ≤ 3cm	A or B	0	
Intermediate (B)	Multinodular	A or B	0	TACE
Advanced (C)	PVI, N1, M1	A	1-2	See Advanced Stage HCC (Figure 2)
End-stage (D)**	Any	C	>2	Best supportive care

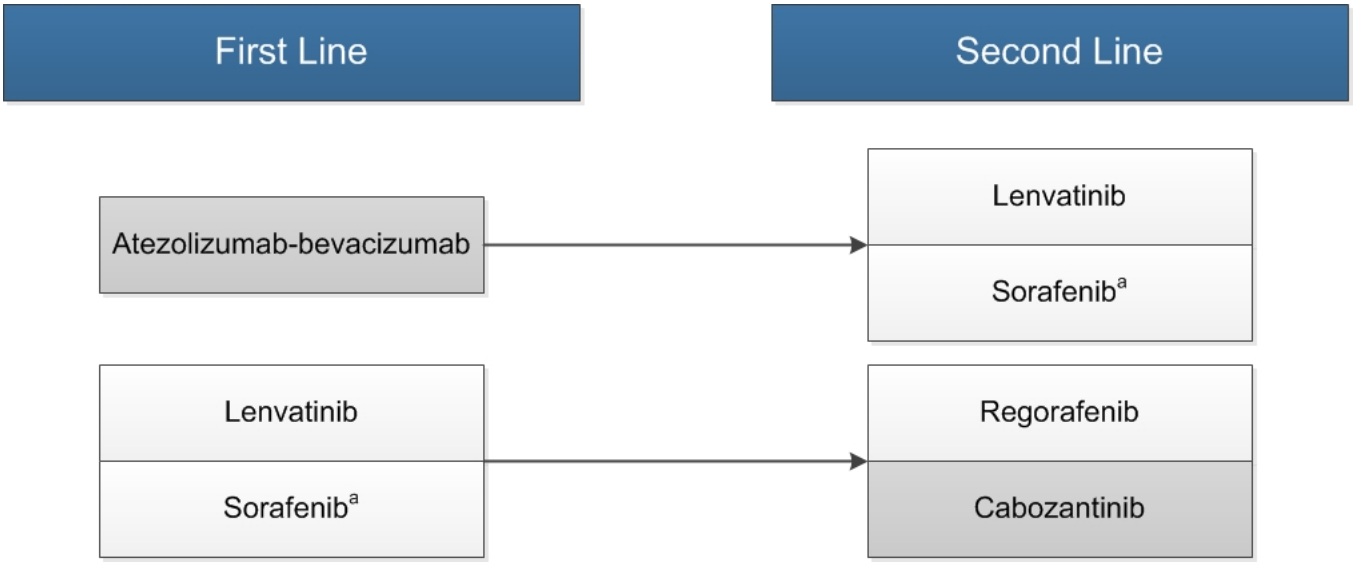
*This table is adapted from Sherman et al. 2011[7] Please see Figure 2 for Alberta specific recommendations for the management of HCC
**Patients who are PVI, N1, M1 and Child-Pugh B or C may be treated as end-stage.
BCLC = Barcelona Clinic Liver Cancer; PS = performance status; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = distant metastasis; PS = Performance Status; RFA = radiofrequency ablation; TACE = transarterial chemoembolization

Figure 1. Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines (adapted from the Alberta[9] and Canadian[8] HCC algorithms).



Milan criteria = single HCC ≤5 cm or 3 HCC largest ≤3 cm, 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 <115 mm^3 and alpha-fetoprotein <400 ng/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; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT =stereotactic body radiotherapy.

Figure 2. Systemic Therapy for Advanced HCC.



Note: Gray boxes indicate drugs which are not funded in Alberta at the time of guideline publication.

Table 4. Definitions, Goals, and Recommendations for Management of Hepatocellular Carcinoma.

Stage	Definitions, Goals, and Recommendations:
Very Early Stage HCC	*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.[10]
	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.[11] • If extra-hepatic disease is confirmed at laparotomy, resection is not pursued. • Intra-operative ultrasound and bi-manual palpation assessment for other intra-hepatic lesions. Intra-operative or subsequent radiofrequency ablation or percutaneous ethanol injection[12, 13] 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.[14, 15] Sorafenib was of no benefit as adjuvant therapy following curative intent resection or radiofrequency ablation (STORM study).[16] • In patients who are not candidates for surgical resection, radiofrequency ablation (see below) can offer a 97% complete response for tumours ≤ 2 cm with long-term survival similar to what has been reported in patients who have undergone resection.[17] • 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[18, 19] whereas one study demonstrated improved recurrence-free and overall survival in the surgical resection group.[20]

	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.[21]
Early Stage HCC	*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:* · To render patient free of disease and to delay or prevent recurrence. *Recommendations:* · Resection (see above), liver transplantation (see below), or ablation[12] (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 up to 10%. • In Alberta, transplantation is contraindicated if the total tumour volume (TTV) exceeds 115 cm^3, the alpha-fetoprotein exceeds 400 ng/mL, vascular invasion and/or extra-hepatic disease exist, or significant co-morbidities exist. • 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.[22, 23]
	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.[24] • Survival rates with radiofrequency ablation may be similar to surgical resection;[18] however, two-year recurrence rates are higher following percutaneous ethanol injection and radiofrequency ablation than with resection.[25] • Best outcomes are achieved from radiofrequency ablation when tumours are centrally located, measure under 3 cm, and are distant from "heat sinks" (blood vessels).[11] 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 HCC	*Patient Requirements:* · Good performance status (ECOG 0-1). · Well-compensated liver function (Child-Pugh class A) and only select patients with impaired liver function (Child-Pugh class B 7). *Tumour Requirements*: · Multinodular disease. · Absence of extra-hepatic disease. · Patency of the main portal vein (as assessed by ultrasound Doppler or MR angiography) for TACE. · Adequate renal function. *Goals:* · 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). · To prolong life, if possible. *Recommendations:* · Transarterial chemo-embolization[26-30] or transarterial radioembolization.[31-34] Consider palliative care if not an LT candidate. *Transarterial Chemo-Embolization (TACE):* • 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®) occludes the relevant branch of the hepatic artery and localizes the chemotherapy. Meta-analyses of randomized controlled trials demonstrate a survival benefit of TACE.[35, 36] Drug-eluting beads

	(DEBs) decrease the systemic exposure to doxorubicin.[37] 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.[29] Recent cohort studies are demonstrating median survival of 4 years after TACE with DEBs in carefully selected patients.[30] *Transarterial Radioembolization (TARE):* • TARE or selective internal radiotherapy (SIRT) uses microspheres 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 (Tc^{99} 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. • A meta-analysis[38] and large cohort studies from Europe[31] and the USA[32] have shown similar survival to TACE in BCLC stage B patients. However, a separate meta-analysis showed superior survival with TACE in unresectable patients.[39] • TARE, unlike TACE, can be performed safely in patients with portal vein thrombosis, as the microspheres used in TARE are smaller and less embolic.[31, 32] • 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.[33, 35] • Outcomes following TARE are best in patients with preserved liver function (Child-Pugh score <8 or MELD score <13).[34] 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 HCC	*Patient Requirements:* · Good performance status (ECOG 0 or 1). · Well-compensated liver function (Child-Pugh class A). *Tumour Requirements*: · Disease ineligible for, or that progressed after, surgical or locoregional therapy. *Goals:* · To maintain or to improve the patient's quality of life (to control or to delay the onset of tumour-related symptoms). · To prolong life, if possible. *Recommendations:* · First-line treatment: Atezolizumab-Bevacizumab , or participation in a clinical trial[36], if available. Lenvitinib or sorafenib should be considered in patients ineligible for or who decline atezolizumab-bevacizumab · Second-line treatment: For patients who received atezolizumab-bevacizumab first-line Lenvatinib or Sorafenib, For patients who received lenvatinib or sorafenib first-line regorafenib or cabozantinib · Third-line: Regorafenib (if previously tolerated Sorafenib), Cabozantinib, or participation in a clinical trial[40], if available. [This is not currently funded] Consider early referral to palliative care Consider referral to dietician and psychosocial
	First-line systemic therapy Child Pugh A • Imaging modality: CT chest, abdomen, and pelvis (triphasic liver) or MRI liver and CT chest. Bone scan if clinically indicated. • Frequency: Every 3 months in the absence of clinical progression. • If not already completed, patients should be screened for hepatitis B/C. Consider a referral to hepatology for patients with cirrhosis and HCC or HBV and HCC. There is evidence suggesting improved outcomes for patients with HCC in the setting of treatment of NAFLD/HBV/HCV cirrhosis.[41] *First-Line Systemic Therapy:* *Atezolizumab-Bevacizumab* (Preferred, Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)[42] • Atezolizumab-bevacizumab was compared to sorafenib in the open-label phase 3 IMbrave150 trial.[43] Hazard ratio for death was 0.58 (95%CI: 0.42-0.79; p<0.001) in favor of atezolizumab-bevacizumab.

Additionally, hazard ratio for disease progression or death was superior in the atezolizumab-bevacizumab arm (HR: 0.59; 95%CI: 0.47-0.76; p<0.001). Overall survival at 12 months was 67% (95%CI: 61.3 to 73.1%) in the atezolizumab-bevacizumab arm compared to 54.6% (95%CI: 45.2-64.0%) in the sorafenib arm. An updated survival analysis showed median overall survival was 19.2 mo with atezolizumab-bevacizumab vs 13.4 months with sorafenib (HR, 0.66 [95% CI, 0.52, 0.85]; *P*=0.0009)[44]

- Grade 3 or 4 adverse events occurred in 56.5% of atezolizumab-bevacizumab patients (n=329) and 55.1% of the sorafenib patients (n=156). Grade 3 or 4 hypertension occurred in 15.2% of atezolizumab-bevacizumab group, however, other high-grade toxic effects were infrequent.
- Treatment with Atezolizumab-Bevacizumab reduced the risk of deterioration in quality of life compared to sorafenib.[45]
- Patients had an ECOG of 0-1, no contraindications to immunotherapy and were not at risk for bleeding. An EGD is strongly recommended within 6 months prior to starting therapy and any varices should be treated (especially if the transient elastography (FibroScan®) >20 kPa or if the platelet count is <150.[46] Patients with incompletely treated varices should not be treated with this combination.
- Atezolizumab-Bevacizumab is not currently funded in Alberta

In those patients where Atezolizumab-Bevacizumab is not appropriate/contraindicated:

Lenvatinib (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)

- Lenvatinib was shown to be non-inferior to sorafenib for overall survival in an open-label, phase 3, multicenter, non-inferiority trial in patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease (median OS 13.6m lenvatinib vs 12.3m sorafenib, respectively, HR: 0.92, 95%CI: 0.79-1.06). Patients had Child Pugh A liver function, and ECOG 0-1.[47]
- It is worth noting that lenvatinib was superior to sorafenib in terms of progression-free survival (7.4m vs 3.7m, respectively, HR: 0.66, 95%CI: 0.57-0.77, p<0.001). Objective response rates were also higher in the lenvatinib group (24.1% vs. 9.2%, respectively, p<0.001).
- Treatment-related adverse events of grade 3 or higher occurred in 57% of patients treated with lenvatinib and 49% with sorafenib. Rates of hand-foot syndrome are lower in the lenvatinib arm compared to sorafenib arm. In the lenvatinib arm, the most common any-grade adverse events included hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%).

or

ECOG 0-2 *Sorafenib* (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)

- Represents an orally active inhibitor of multiple cell surface tyrosine kinases (e.g.: VEGFR, PDGFR-ß, *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:

End-Point	SHARP Trial[48]		Asia-Pacific Trial[49]	
	Sorafenib	Placebo	Sorafenib	Placebo
Median Survival	10.7 months	7.9 months	6.5 months	4.2 months
	HR 0.69 ($CI_{95\%}$ 0.55-0.87) $p < 0.001$		HR 0.68 ($CI_{95\%}$ 0.50-0.93) $p < 0.014$	
Time to Progression (Radiologic)	5.5 months	2.8 months	2.8 months	1.4 months
	HR 0.58 ($CI_{95\%}$ 0.45-0.74) $p < 0.001$		HR 0.57 ($CI_{95\%}$ 0.42-0.79) $p = 0.0005$	

- 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.[35, 50]
- Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, $p = 0.015$).[36]

Second-Line Systemic Therapy:

Lenvatinib (if not received in the first-line)

- There is no level 1 evidence to inform the most effective treatment after atezolizumab plus bevacizumab. The most common second line therapies received by patients in the IMbrave150 trial were sorafenib (n=31)

and lenvatinib (n=22). It would be reasonable to treat patients with lenvatinib after atezolizumab-bevacizumab.

Second line trials for HCC were conducted after prior treatment with sorafenib. It would be reasonable to use the agents below if patients were treated with lenvatinib instead of sorafenib.[*]

Regorafenib

- Regorafenib has been shown to be superior to placebo for survival, progression-free survival and objective response in HCC patients who previously progressed on and who tolerated sorafenib
- The RESORCE trial[51] randomized (2:1) adult HCC patients, Child Pugh A liver function, ECOG 0-1, who tolerated sorafenib at a dose of ≥20 of last 28 days of treatment and who progressed on sorafenib to receive regorafenib or placebo.
- Median overall survival was 10.6 months with regorafenib vs. 7.8 months with placebo (HR for death: 0.63; 95%CI: 0.50-0.79, p<0.001).
- Median progression-free survival was 3.1 months with regorafenib and 1.5 months with placebo (HR 0.46; 95% CI 0.37-0.56, p<0.0001).
- The most common high-grade adverse events associated with regorafenib were hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and diarrhea (3%).

Cabozantinib

- Cabozantinib was shown to be superior to placebo for survival, progression-free survival and objective response in Child Pugh A HCC patients who previously received sorafenib.
- The CELESTIAL trial[52] randomized (2:1) eligible patients who had received prior treatment with sorafenib, and had disease progression after at least one systemic treatment for HCC to receive cabozantinib or placebo.
- Median overall survival was 10.2 months with cabozantinib and 8.0 months with placebo (HR for death: 0.76; 95%CI: 0.63-0.92, p=0.005).
- Median progression-free survival was 5.2 months with cabozantinib vs. 1.9 months with placebo (p<0.001).
- The most common high-grade adverse events associated with cabozantinib were palmar-plantar erythrodysesthesia (17%), hypertension (16%), increased aspartate aminotransferase level (12%), fatigue (10%) and diarrhea (10%).
- Cabozantinib is not yet publicly funded.

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.[53]
- 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[54] and to bridge patients to liver transplantation.[55]
- 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 SBRT[54] 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.

[*] Type: Informal consensus, benefits may outweigh harms; Evidence quality: low to moderate; Strength of recommendation: weak.

Terminal Stage HCC	*Patient Requirements:*	· Poor performance status (ECOG > 2). · Decompensated liver function (Child-Pugh class B and C).
	Goals:	· To maintain or to improve the patient's quality of life (to control tumour-related symptoms).
	Recommendations:	· Best supportive care [Link]. · Palliative chemotherapy may adversely affect outcome.[56]

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Appendix A: TMN Staging System for HCC, AJCC Eighth Edition

Stage	Tumour Description		Regional* Lymph Node Involvement		Distant Metastases	
Stage I_A	T1a	Solitary tumor ≤2 cm	N_0	Absent	M_0	Absent
Stage I_B	T1b	Solitary tumor >2 cm without vascular invasion	N_0	Absent	M_0	Absent
Stage II	T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm	N_0	Absent	M_0	Absent
Stage III_A	T3	Multiple tumors, at least one of which is >5 cm	N_0	Absent	M_0	Absent
Stage III_B	T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	N_0	Absent	M_0	Absent
Stage IV_A	Any		N1	≥1 positive node	M_0	Absent
Stage IV_B	Any		Any		M_1	Present

Appendix B: ECOG Performance Status Scale

ECOG	Description
0	Fully active and able to carry on without restriction.
1	Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care and/or confined to a bed or chair for more than 50% of waking hours.
4	Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.

Appendix C: Child-Pugh Classification System

Criteria	Score 1 Point	Score 2 Points	Score 3 Points
Encephalopathy	Grade 0	Grade 1 or 2 (or suppressed with medications)	Grade 3 or 4 (or refractory)
Ascites	None	Suppressed with medications	Refractory
Bilirubin	Under 34 µmol	Between 34 at 50 µmol	Over 50 µmol
Albumin	Over 35 g/L	Between 28 and 35 g/L	Under 28 g/L
PT-INR	Under 1.7	Between 1.7 and 2.2	Over 2.2
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”	

Appendix D: Systemic Therapy Dosing

Agent(s)	Dose
Atezolizumab-bevacixumab	1200 mg Atezolizumab plus 15 mg/kg body weight bevacizumab IV q3 weekly
Lenvatinib	12 mg po daily (for bodyweight ≥60 kg) or 8 mg po daily (for bodyweight <60 kg)
Sorafenib	400 mg po BID
Regorafenib	50 mg/day po daily during weeks 1-3 of each 4 week cycle
Cabozantinib	60 mg po daily

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial GI Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, gastroenterologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial GI Tumour Team, external participants identified by the Working Group Lead, and a methodologist 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 2009.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AASLD, American Association for the Study of Liver Disease; ACR, American College of Radiology; AHS, Alberta Health Services; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; CI, confidence interval; CT, computed tomography; DEB, drug-eluting bead; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; MDT, multidisciplinary team; MR, magnetic resonance; MELD, Model for End-stage Liver Disease; PEI, percutaneous ethanol injection; PO, by mouth, orally; PS, performance status, RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemo-embolization; TARE, transarterial radioembolization; TNM, tumour-node-metastasis; TSH, thyroid stimulating hormone; TTV, total tumour volume; US, ultrasound; US LI-RADS, ultrasound liver imaging reporting and data system.

Disclaimer

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.

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Conflict of Interest Statements

Dr. Kelly Burak has nothing to disclose.

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