

Hepatocellular Carcinoma

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Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, and the third leading cause of cancer related mortality.¹ It is the most common type of liver cancer, and in 85-90% occurs in the setting of underlying cirrhosis. Cirrhosis represents a diffuse liver disease characterized by structurally abnormal nodules of liver cells surrounded by fibrosis.² It results from chronic liver injury and regeneration secondary to chronic viral hepatitis, alcoholic-related liver disease, metabolic-dysfunction associated steatotic liver disease (MASLD, formally known as non-alcoholic fatty liver disease), genetic liver diseases (e.g. hemochromatosis, Wilson's disease, α_1 -antitrypsin deficiency), and autoimmune diseases (e.g. autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis). Cirrhosis is associated with an annual incidence of hepatocellular carcinoma of 2 to 5 percent.³ Of note, patients with MASLD and patients with chronic hepatitis B virus infection can develop HCC in the absence of cirrhosis.

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 the tumor burden, the α -fetoprotein (AFP) level, the patient's performance status (see Appendix B), the histologic subtype (e.g. fibrolamellar variant), and the degree of liver dysfunction (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 2023 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2023 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 α -fetoprotein (AFP) is recommended every six months.² 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 chronic 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, it is also recommended in patients with family history of HCC and in patients with a PAGE-B score ≥ 10 (Appendix D).⁴ 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.⁵ 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.⁵

Table 1: US LI-RADS for Surveillance^{5, 6}

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 or 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 AASLD². 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.⁷ 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.⁸ 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.

Recent study from Alberta, found that contrast-enhanced US (CEUS) performed better than MRI for evaluating lesions >1 cm found on surveillance US.⁹ Therefore, CEUS (if available) can be considered as the first study to evaluate nodules found on surveillance US, and biopsy can be reserved for those with discordant imaging or when intrahepatic cholangiocarcinoma is suspected.¹⁰

Table 2: Summary of CT/ MRI LI-RADS categories⁷

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 major features OR - 10-19 mm with $\geq 50\%$ size increases in ≤ 6 months and no other major features OR - ≥ 20 mm with ≥ 1 additional major feature

Diagnostic Category	Conceptual Definition	CT/MRI Criteria
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.⁸ Likewise, LIRADS has not been validated in patients with cirrhosis due to vascular etiologies, such as cardiogenic cirrhosis or Budd Chiari Syndrome, and in such cases liver biopsy is also recommended.³

Goals and Recommendations

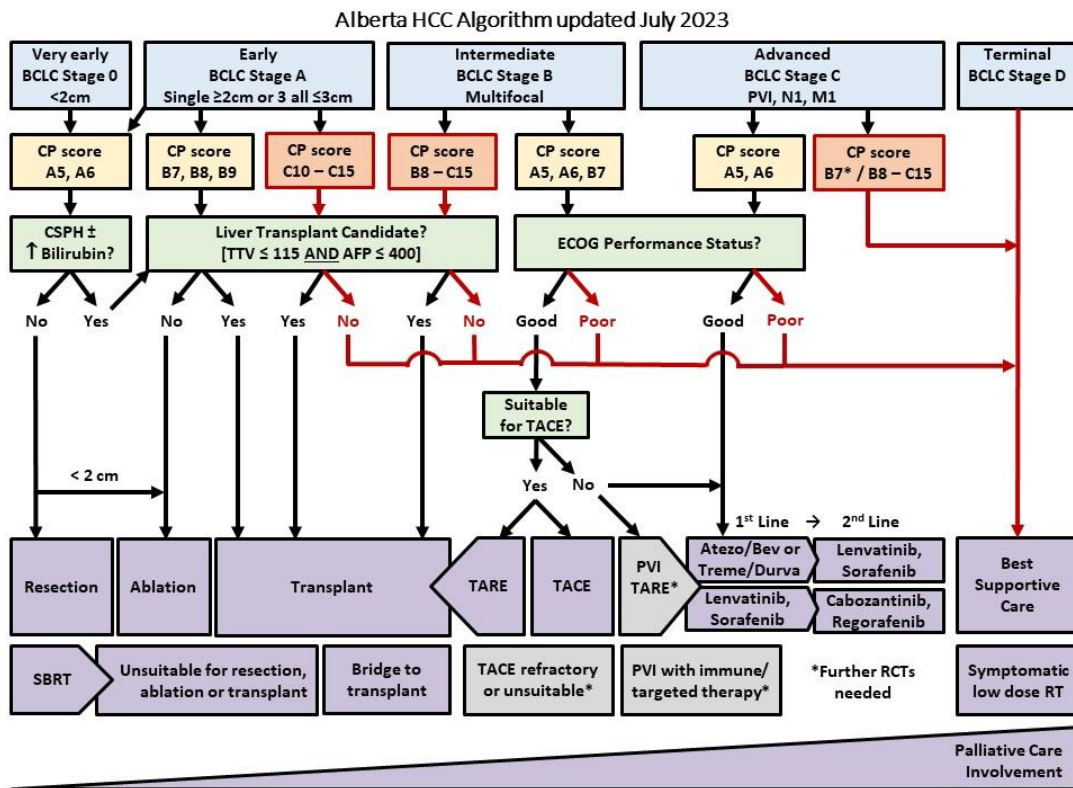


Figure 1. Alberta HCC Algorithm. Reproduced with permission from Dr. K. Burak.

To define and provide optimal care to a patient with HCC, a multidisciplinary team (MDT) is required. It should include, but is not limited to, hepatobiliary surgeons, diagnostic and interventional radiologists, hepatologists/gastroenterologists, radiation oncologists, 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.^{11, 12} 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 recommendations given in this clinical practice guideline is provided (Figure 1).

Consider treatment on a clinical trial, if available.

Table 3. Barcelona Clinic Liver Cancer Staging System.¹³

BCLC Stage	Tumour Stage	Liver function	ECOG PS	Therapy options recommended ⁷
Very early (0)	Single ≤ 2cm	Preserved	0	Resection or Transplantation or Ablation or TARE or TACE or SBRT
Early (A)	Single, Or up to three all ≤ 3cm	Preserved	0	
Intermediate (B)	Multinodular	Preserved	0-1	TACE or TARE or SBRT
Advanced (C)	PVI, N1, M1	Preserved	1-2	See Advanced Stage HCC (Figure 2)
End-stage (D)**	Any	Non-preserved	>2	Best supportive care Palliative radiotherapy

*This table is adapted from Sherman et al. 2011⁷ 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

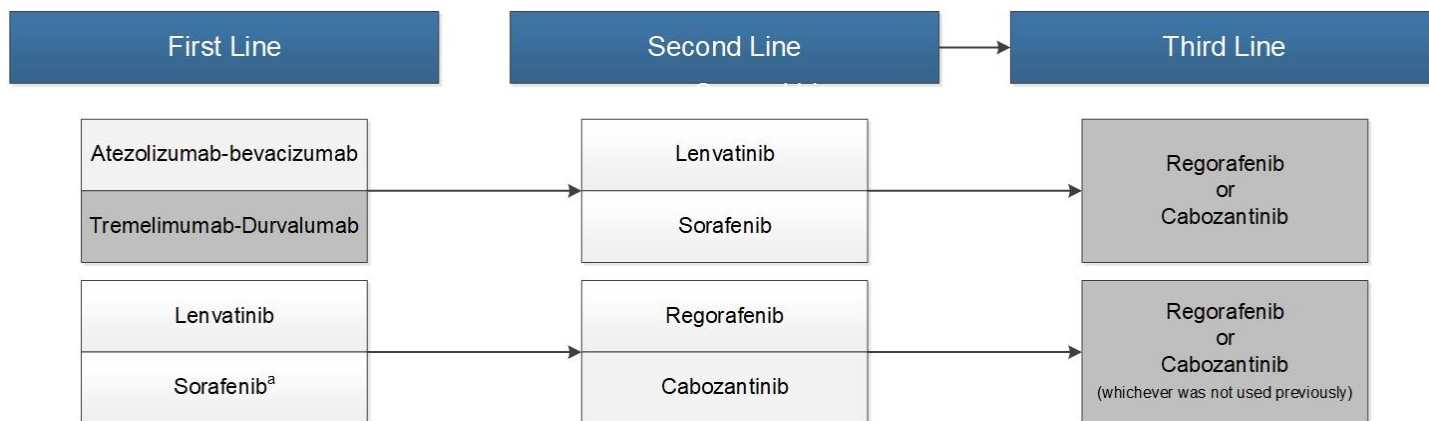


Figure 2. Systemic Therapy for Advanced HCC.

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	<p><i>Patient Requirements:</i></p> <ul style="list-style-type: none"> • Good performance status (ECOG 0). • Preserved liver function <p><i>Tumour Requirements:</i></p> <ul style="list-style-type: none"> • 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. <p><i>Goals:</i></p> <ul style="list-style-type: none"> • To render patient free of disease and to delay or prevent recurrence. <p><i>Recommendation:</i></p> <ul style="list-style-type: none"> • Resection, ablation. Alternatives: TARE, and SBRT.¹² <p><i>Resection:</i></p> <ul style="list-style-type: none"> • 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 <i>de novo</i> tumour development. • Abnormal bilirubin and clinically significant portal hypertension (as suggested by thrombocytopenia with platelet count under 100, varices, ascites, and/or splenomegaly) predict for failure to benefit from resection.¹⁴ • In patients with cirrhosis, an estimated future liver remnant of $\geq 40\%$ is needed before proceeding to surgical resection. In patients with a smaller volume, strategies such as portal vein embolization and/or radiation lobectomy with TARE can be employed to enhance hypertrophy of the residual volume. The most common TARE strategy in this setting is with single compartment dosimetry, with a lobar infusion of 140-150 Gy.^{15, 16} TARE may be a preferred strategy when a biologic test-of-time is needed before resection, such as in cases with high AFP, in infiltrative-appearing tumors, or in bulky tumors and/or with satellites. • 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^{17, 18} can be considered for multicentric disease. • No clear benefit has been established for adjuvant sorafenib post-resection. In fact, adjuvant chemotherapy may adversely affect the outcome, especially in cirrhotic patients.^{16, 17} Sorafenib was of no benefit as adjuvant therapy following curative intent resection or radiofrequency ablation (STORM study).¹⁸ The IMbrave050 study¹⁹ in which patients considered at high risk of recurrence after ablation or resection were randomized to Atezolizumab/Bevacizumab or active surveillance, demonstrated superior recurrence-free survival with the adjuvant therapy, but overall survival results were immature at the time of publication. Therefore, the current recommendation is active surveillance only.

	<ul style="list-style-type: none"> 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.²⁰ 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^{21, 22} whereas one study demonstrated improved recurrence-free and overall survival in the surgical resection group.²³ In patients that are not candidates for ablation or resection, segmentectomy with TARE is an alternative. Radiation segmentectomy is usually based on single compartment dosimetry, aiming for a dose of 400 Gy. The LEGACY and the RASER studies demonstrated that this approach is associated with objective response rates of up to 100%.²⁴⁻²⁷ For patients with liver-confined HCC who are not candidates for curative options (surgery or thermal ablation) and for whom catheter-based therapies are being considered, EBRT is recommended as a potential first-line single therapy option.²⁸ See details regarding RTOG 1112 and other relevant trials in Appendix G. <p><i>Follow-Up:</i> 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.²⁹</p>
Early Stage HCC	<p><i>Patient Requirements:</i></p> <ul style="list-style-type: none"> Good performance status (ECOG 0). Preserved liver function <p><i>Tumour Requirements:</i></p> <ul style="list-style-type: none"> 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. <p><i>Goals:</i></p> <ul style="list-style-type: none"> To render patient free of disease and to delay or prevent recurrence. <p><i>Recommendations:</i></p> <ul style="list-style-type: none"> Resection (see above), liver transplantation (see below), ablation¹⁴ (see below). <p>Alternatives: TACE, TARE, and SBRT</p> <p><i>Liver Transplantation:</i></p> <ul style="list-style-type: none"> 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 (and recurrence rate) of less than 10-15%. In Alberta, transplantation is contraindicated if the total tumour volume (TTV) exceeds 115 cm³, 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 cm³ and both the total tumour volume and the AFP remain under 115 cm³ and 400 ng/mL, respectively, for more than six months.^{30, 31} <p><i>Radiofrequency Ablation (RFA) or Microwave Ablation or Percutaneous Ethanol Injection (PEI):</i></p> <ul style="list-style-type: none"> 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.³² Survival rates with radiofrequency ablation may be similar to surgical resection;²¹ however, two-year recurrence rates are higher following percutaneous ethanol injection and radiofrequency ablation than with resection.³³ Microwave ablation is a valid alternative to RFA³⁴ and may be less impacted by heat sink effect. Best outcomes are achieved from radiofrequency ablation when tumours are centrally located, measure under 3 cm, and are distant from “heat sinks” (blood vessels).¹⁴ Consider percutaneous ethanol injection or transarterial chemo-embolization (TACE) when tumours are in a subcapsular location, exceed 3 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). <p>TARE</p> <ul style="list-style-type: none"> In patients that are not candidates for ablation or resection, segmentectomy with TARE is a valid alternative with curative potential for single tumors of up to 8 cm. Radiation segmentectomy is usually

	<p>based on single compartment dosimetry, aiming for a dose of 400 Gy. The LEGACY and the RASER studies demonstrated that this approach is associated with objective response rates of up to 100%.²⁴⁻²⁷</p> <ul style="list-style-type: none"> • Lesions in which TARE can offer benefits compared to ablations, are those larger than 3 cm, or those in which ablation is not technically possible (lesions near the hilum, lesions in the dome, or in the caudate lobe, or next to other organs/structures or major vessels). <p>SBRT²⁸</p> <ul style="list-style-type: none"> • For patients with liver-confined HCC who are not candidates for curative options (surgery or thermal ablation) and for whom catheter-based therapies are being considered, EBRT is recommended as a potential first-line single therapy option.²⁸ See details regarding RTOG 1112 and other relevant trials in Appendix G. • Meta-analysis found no statistically significant difference in LC or OS between ultrahypofractionated EBRT and RFA • Common reasons why thermal ablation would be technically suboptimal include lack of ultrasound echogenicity/visibility, relatively large tumor size (>3 cm), and tumor location in close proximity to a large vessel that may result in a heat sink, diaphragm, or gallbladder
Intermediate Stage HCC	<p>Patient Requirements:</p> <ul style="list-style-type: none"> • Good performance status (ECOG 0-1). • Preserved liver function <p>Tumour Requirements:</p> <ul style="list-style-type: none"> • Multinodular disease (<i>i.e.</i> more than 3 nodules or 2-3 nodules in which at least one of them is larger than 3 cm) • Absence of extra-hepatic disease and tumor thrombus • Patency of the main portal vein (as assessed by ultrasound Doppler or MR angiography) for TACE. • Adequate renal function. <p>Goals:</p> <ul style="list-style-type: none"> • 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. +In selected cases, to downstage patients to LT criteria <p>Recommendations:</p> <p>Transarterial chemo-embolization³⁵⁻³⁹ or transarterial radioembolization.⁴⁰⁻⁴³ Considered palliative therapy if not an LT candidate.</p> <ul style="list-style-type: none"> • Systemic therapy as described below in the Advanced Stage HCC section is recommended if patients are not eligible for locoregional therapies <p>Transarterial Chemo-Embolization (TACE):</p> <p>Meta-analyses of randomized controlled trials demonstrate a survival benefit of TACE.^{44, 45} Drug-eluting beads (DEBs) decrease the systemic exposure to doxorubicin.⁴⁰ 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.³⁸ Recent cohort studies are demonstrating median survival of 4 years after TACE with DEBs in carefully selected patients.³⁹ The RTOG 1112 RCT⁴⁶ included patients with locally advanced HCC unsuitable for resection, RFA, TACE. 80% of patients had BCLC stage B or C disease. The sum of HCC diameters had to be less than 20cm. Patients were randomized to Sorafenib vs Sorafenib and SBRT. 193 patients were randomized. 74% of patients had macrovascular invasion and median sum of maximum diameter of HCC lesions was 7.6cm.</p> <ul style="list-style-type: none"> • Median Overall survival was 12.3 months with sorafenib and 15.8 months with SBRT and sorafenib (p = 0.055). Median PFS was 5.5 vs 9.2 months (P < 0.01). There was no significant difference in grade 3 or higher adverse events. • Systemic therapy as described below in the Advanced Stage HCC section is recommended if patients are not eligible for TACE.

	<p>Transarterial Radioembolization (TARE): TARE can be used as an alternative to TACE in initial treatment of intermediate-stage, unresectable HCC patients as it may offer benefits of lower toxicity, and assist in downsizing to curative intent as well as bridging to transplant.⁴⁷</p> <ul style="list-style-type: none"> ●TARE, unlike TACE, can be performed safely in patients with portal vein thrombosis, as the microspheres used in TARE are smaller and less embolic.^{25, 40, 41} ●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.^{42, 44} ●Outcomes following TARE are best in patients with preserved liver function (Child-Pugh score <8 or MELD score <13).³⁷ Patients should be selected for TARE at MDT meetings. <p>-The Dosisphere study, a randomized, multicenter, phase 2 trial that compared personalized versus standard dosimetry showed the importance of using multicompartiment dosimetry. Treatment should aim for a TAD of ≥ 205 Gy (>250 Gy, when possible) and a non-TAD of ≤ 120 Gy in order maximize tumor dose and preserve liver function (Garin E, et al. Lancet Gastroenterol Hepatol 2020) (Baker T, et al. HPB, 2021) (Salem R, et al. Eur J Nucl Med Mol Imaging, 2021).^{16, 48} The association between TAD and response rate was further confirmed in the TAGET study, a multicenter, retrospective, cohort study (Lam M, et al. Eur J Nucl Med Mmol Imaging 2022).⁴⁹</p> <ul style="list-style-type: none"> ●When considering TACE versus TARE, trials that compare the two strategies have shown superiority of TARE in terms of time to progression, but not clear advantages in terms of overall survival (Kolligs FT, et al. Liver Int 2015) (Salem R, et al. Gastroenterology 2016). However, the most recent trial, which is the TRACE trial, did show longer overall survival in the group that received TARE compared to TACE (Dhondt E, et al. Radiology, 2022.). Of note, all these trials have used single compartment dosimetry, which is now not the standard.
EBRT IN DEFINITIVE/NON-TRANSPLANT SETTING	<p>For patients with liver-confined multifocal and/or unresectable HCC, EBRT alone or sequenced with other catheter-based therapies* is conditionally recommended.²⁸</p> <p>For patients with liver-confined HCC who had an incomplete response to thermal ablation or catheter-based therapies,* EBRT is recommended as a consolidative treatment option.²⁸</p> <p>For patients with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies,* EBRT is recommended as a salvage treatment option.²⁸</p> <p>For patients with liver-confined HCC with macrovascular invasion, EBRT is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies. (Caution should be used when recommending EBRT after TARE until more data is available.²⁸</p> <p>For patients with liver-confined HCC who had an incomplete response to thermal ablation or catheter-based therapies, EBRT is recommended as a consolidative treatment option. Strength of recommendation (Strong) Quality of Evidence Moderate</p> <p>For patients with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies, EBRT is can be considered as a salvage treatment option. Quality of evidence Low</p> <p>For patients with liver-confined HCC with macrovascular invasion, EBRT can be considered, alone or sequenced with systemic therapy or catheter-based therapies Quality of evidence (Moderate)</p> <p>See Radiation Appendix [here]</p>
Advanced Stage HCC	<p><i>Patient Requirements:</i></p> <ul style="list-style-type: none"> • Good performance status (ECOG 0 or 1). • Well-compensated liver function (Child-Pugh class A). <p><i>Tumour Requirements:</i></p> <ul style="list-style-type: none"> • Disease ineligible for, or that progressed after, surgical or locoregional therapy. <p><i>Goals:</i></p> <ul style="list-style-type: none"> • To maintain or to improve the patient's quality of life (to control or to delay the onset of tumour-related symptoms). • To prolong survival, if possible.

Recommendations:

- First-line treatment: Atezolizumab-Bevacizumab⁵⁰, Tremelimumab-Durvalumab⁵¹ (STRIDE) or participation in a clinical trial, if available. Lenvatinib or sorafenib should be considered in patients ineligible for or who decline atezolizumab-bevacizumab or STRIDE [note Tremelimumab-Durvalumab (STRIDE) is not currently funded in Alberta].
 - Second-line treatment: For patients who received atezolizumab-bevacizumab or tremelimumab-durvalumab (STRIDE) first-line, second-line treatment should be lenvatinib or sorafenib, For patients who received lenvatinib or sorafenib first-line, second-line treatment should be regorafenib or cabozantinib.
 - Third-line: Regorafenib (if previously tolerated Sorafenib), Cabozantinib, or participation in a clinical trial⁵¹, if available. [Third line therapy is currently not funded in Alberta]
- Consider early referral to palliative care. Consider referral to dietician and for psychosocial support.

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 HBV or HCV. There is evidence suggesting improved outcomes for patients with HCC in the setting of treatment of NAFLD/HBV/HCV cirrhosis.⁵³

First-Line Systemic Therapy:

Atezolizumab-Bevacizumab (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)^{50, 52}

- Atezolizumab-bevacizumab was compared to sorafenib in the open-label phase 3 IMbrave150 trial.⁵⁰ 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)⁵³
- 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.⁵⁴
- 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 varices should be treated according to the standard practice⁵⁵ (especially if the transient elastography (FibroScan®) >20 kPa or if the platelet count is <150).⁵⁶ Patients with incompletely treated varices should not be treated with this combination.

Tremelimumab-Durvalumab (STRIDE) Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)⁵⁷

- Tremelimumab plus durvalumab in an infusion regimen termed STRIDE (Single Tremelimumab Regular Interval Durvalumab) were compared to durvalumab or sorafenib alone in the open-label, phase 3, HIMALAYA trial. Median OS was 16.4m (95%CI: 14.2-19.6) with STRIDE, and 13.8m (95%CI: 12.3-16.1) with sorafenib. Risk of death was lower with STRIDE compared to sorafenib; HR: 0.78(95%CI: 0.65-0.93; p=0.0035). Median PFS was not significantly different between treatment arms.
- Grade 3/4 treatment-emergent adverse events occurred for 50.5% of patients with STRIDE, and 52.4% with sorafenib.

In those patients where Atezolizumab-Bevacizumab or STRIDE 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 0-1.⁵⁸
- 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- 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.^{59, 60}
- 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.^{44, 61}
- Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, $p = 0.015$).⁴⁵

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 trial⁶² 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.

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

	<ul style="list-style-type: none"> • The CELESTIAL trial⁶³ 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%).
Terminal Stage HCC	<p><i>Patient Requirements:</i></p> <ul style="list-style-type: none"> • Poor performance status (ECOG > 2). • Decompensated liver function (Child-Pugh class B and C). <p><i>Goals:</i></p> <ul style="list-style-type: none"> • To maintain or to improve the patient's quality of life (to control tumour-related symptoms). <p><i>Recommendations:</i></p> <ul style="list-style-type: none"> • Best supportive care [Link]. • Palliative chemotherapy may adversely affect outcome.⁶⁴ <p>Palliative radiation</p> <p>The CCTG HE.1 RCT⁴⁶ included patients with painful HCC or liver metastases. Patients were randomized with best supportive care or 8 Gy in 1 fraction. 66 patients were randomized, 23 with HCC. 59% of patients had an ECOG of 2-3 and 35% had CP B or C cirrhosis. The CTV included the whole liver or near whole liver. The primary endpoint showed significant improvement in worst pain score at 1 month. 67% of patients on RT and 22% on best supportive care had a significant improvement (p=0.004). The secondary endpoint of 3-month OS trended to improvement with palliative RT (51% vs 33%, p=0.07). Patients with painful HCC should be considered for palliative RT.</p>

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

Stage	Tumour Description		Regional* Lymph Node Involvement		Distant Metastases	
			N ₀	Absent	M ₀	Absent
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/ALBI Grade Classification Systems

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”

Note the Child-Pugh classification system has been abandoned for the evaluation of liver function in the BCLC.⁶⁶

ALBI Score	ALBI Grade	Median Survival (m) for Newly Diagnosed HCC Patient*	Median Survival (m) in Patients with Prior Sorafenib**
≤-2.6	A1	85.6	12.7
>-2.6 and ≤-1.39	A2	46.5	7.2
>-1.39	A3	15.5	3.6

ALBI_score = (log(Bilirubin[mcmol/L]) * 0.66) - (Albumin[g/L] * 0.085)

*Median Survival for all HCC patients including those who later had potentially curative surgery.²⁸

**Median survival for HCC patients with unresectable or relapsed incurable disease.

Appendix D: PAGE B Score

Age	Points	Sex	Points	Platelets	Points
16-29	0	F	0	>200	0
30-39	2	M	6	100-200	6
40-49	4			<100	9
50-59	6				
60-69	8				
≥70	10				

Appendix E: Systemic Therapy Dosing

Agent(s)	Dose
Atezolizumab-bevacizumab	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

Appendix F: TARE/ TACE Definition

TARE

TARE or selective internal radiotherapy (SIRT) uses microspheres loaded with yttrium-90 (Y90) 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 technetium-99 macro-aggregated albumin (Tc99 MAA). At the same time selective embolization of the gastroduodenal arteries is carried out if needed to prevent delivery of radiation to the stomach and duodenum. The procedure may be repeated depending upon response.

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.

Appendix G:

The TRENDY RCT⁶⁵ included patients eligible for TACE and were randomized to TACE-DEB vs. SBRT. 30 patients were randomized. At median follow up of 28 months, the time to progression was similar (12 vs 19 months for TACE-DEB vs SBRT, $p = 0.15$). Secondary endpoints showed trend towards improved local control (12 vs 40 months, $p=0.07$), improved median OS (36.8 vs 44.1 months), 2-year local control (43.6 vs 100%), no few grade 3 or higher adverse events and stable quality of life in both arms.

The Bush RCT⁶⁶ included patients with untreated HCC meeting the Milan or San Francisco transplant criteria. Patients were randomized to TACE or proton beam therapy. TACE was repeated until complete or maximal response. 76 patients were randomized. 2-year OS was similar at 68%. Median PFS was significantly improved (12 months vs not reached, $p = 0.0002$), local control was better with SBRT (HR 5.64, $p = 0.03$) and days of hospitalization after treatment was significantly reduced with SBRT (166 vs 24 days, $p < 0.01$).

The Comito RCT⁶⁷ included patients with an incomplete response to a prior TAE/TACE. Patients were randomized to repeat TAE/TACE vs SBRT. 40 patients were enrolled. The primary endpoint of LC was improved with SBRT (8 months vs not reached, $P < 0.01$). 2-year PFS (6 vs 21%), OS (57 vs 64%) favored SBRT. There were no grade 3 or higher adverse events in either arm. SBRT should be considered in patients with an incomplete response to TAE/TACE.

- Median Overall survival was 12.3 months with sorafenib and 15.8 months with SBRT and sorafenib ($p = 0.055$). Median PFS was 5.5 vs 9.2 months ($P < 0.01$). There was no significant difference in grade 3 or higher adverse events.

For SBRT, data suggest that there might not be a dose-response relationship within the range of reported schedules (33-60 Gy, 3-5 fractions, BED 60-180 Gy¹⁰). However, it is difficult to tease apart dose and volume factors.⁶⁸

In contrast to RTOG 1112, 3 consecutive RCTs comparing TARE with sorafenib in advanced-stage HCC failed to meet the primary endpoint of superior OS.⁶⁹⁻⁷¹

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 2025. 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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