



Guideline 2-24

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Non-Surgical Management of Advanced Hepatocellular Carcinoma

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An assessment conducted in December 2022 deferred the review of Guideline 2-24. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document

[\(PEBC Assessment & Review Protocol\)](#)

Guideline 2-24 consists of 5 sections. You can access the summary and full report here: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/59651>

- Section 1: Recommendations
- Section 2: Guideline - Recommendations and Key Evidence
- Section 3: Guideline Methods Overview
- Section 4: Systematic Review
- Section 5: Internal and External Review

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PUBLICATIONS RELATED TO THIS REPORT

1. Baldassarre FG, Baerlocher M, Beecroft R, Dawson L. Focal Tumour ablation: thermal ablation of hepatocellular carcinoma and metastases from colorectal carcinoma: evidence summary [Internet]. Cancer Care Ontario; 2014 Jul [cited 2014 Jul 28]. Available from: <https://www.cancercare.on.ca/>.

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Non-Surgical Management of Advanced Hepatocellular Carcinoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES

The objective of this guideline is to make recommendations regarding the non-surgical treatment of advanced hepatocellular carcinoma (HCC).

TARGET POPULATION

These recommendations apply to adults with locally advanced and advanced HCC, Barcelona Clinic Liver Cancer Stage B and higher, who are not suitable for transplant or surgery.

INTENDED USERS

Intended users of the guideline are clinicians involved in the care of patients who have HCC; specifically, medical oncologists, radiation oncologists, interventional radiologists, hepatologists, and surgical oncologists.

RECOMMENDATIONS

Recommendation 1
There is insufficient evidence for or against the use of TEA, TAE, RFA, TARE, SBRT, or DEB-TACE instead of TACE, which has been the conventional standard of care, in patients with intermediate-stage HCC or higher to improve survival. Decisions regarding treatment should be made on a case-by-case basis. Each case should be evaluated separately at a multidisciplinary cancer conference (MCC) that includes medical oncologists, radiation oncologists, surgical oncologists, hepatologists, and interventional radiologists. Short-term follow-up data indicate that TARE may result in less toxicity than TACE but longer-term follow-up data are not available.
Qualifying Statements for Recommendation 1
- For the treatment of intermediate-stage or greater HCC, treatment decisions will depend largely on Child-Pugh score, location of disease, volume of disease, and the number of lesions. - Typically, patients with early-stage disease not amenable to surgery may be treated with RFA or one of the other local/regional therapies. If that treatment fails, they may be treated with TACE for some of their lesions but may also be treated with other local/regional therapies for specific other lesions. - Failure to benefit from prior local/regional therapies should trigger early consideration of systemic treatments. - In addition, recent abstract data from the large international OPTIMIS [1] study show an improvement in overall survival (OS) for patients with an early start to sorafenib therapy at the time of meeting standard TACE ineligibility compared with no sorafenib

at that time of TACE ineligibility. This study also demonstrates that in a real-world experience, deviations from treatment guidelines for TACE and not starting sorafenib (systemic therapy) are common and detrimental. In addition, patient selection is extremely important for TACE. Comorbidities, liver function (beyond Childs Pugh A) and patient performance status (ex. ECOG) need to be thoroughly assessed.

- The decision to stop TACE and move on to systemic therapy can be challenging and should be made on a case-by-case basis at an MCC. Treating patients who were not responsive to TACE or are TACE ineligible may make them ineligible to benefit from systemic therapy.
- Further randomized data would be required to make more definitive statements about the use of local/regional therapies compared with TACE.

Recommendation 2

- There is insufficient evidence to support the addition of sorafenib to local/regional therapies to improve survival in patients with intermediate or higher stage HCC.

Qualifying Statements for Recommendation 2

- Following failure of local therapies, suitable patient (Child-Pugh A, Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0-2) should be considered for treatment with systemic therapy.

Recommendation 3

- There are currently two tyrosine kinase inhibitors (sorafenib and lenvatinib) recommended as first-line single-agent systemic therapy that have survival benefits.
- There is no evidence to support the use of sorafenib or lenvatinib in combination with other agents with respect to objective outcomes (OS, objective response rate, toxicity) in patients with advanced HCC.

Qualifying Statements for Recommendation 3

- It should be noted that in the lenvatinib trial [2] patient inclusion criteria were stricter than in the SHARP [3] sorafenib trial with respect to performance status (ECOG PS 0-1 in the lenvatinib trial vs. ECOG PS 0-2 in SHARP) and main portal vein thrombosis (excluded in the lenvatinib trial vs. included in SHARP).
- Since the side effect profiles of sorafenib and lenvatinib differ, it is conceivable that if a patient does not tolerate one drug in the first-line setting, they could be switched to the other drug prior to progression.
- A phase III trial of nivolumab vs. sorafenib (CheckMate 459) is ongoing and this recommendation should be revisited once the data from this trial are available.

Recommendation 4

- There are currently two tyrosine kinase inhibitors (regorafenib and cabozantinib) given as second-line therapy after sorafenib that have survival benefits and are treatment options for patients with advanced HCC with preserved liver function and who are otherwise well.

Qualifying Statements for Recommendation 4

- The modest survival benefit of these drugs needs to be weighed against the side effects incurred.
- For second-line therapy, the cabozantinib trial included patients who did not tolerate sorafenib, whereas in the regorafenib trial, patients were required to tolerate a minimum dose of 400 mg for $\geq 21/28$ days previously. None of the second-line trials specifically address lenvatinib; however, for patients who progress on lenvatinib, either second-line agent is reasonable.
- Since the side effect profiles of regorafenib and cabozantinib differ, it is conceivable that if a patient does not tolerate one drug in the second-line setting, they could be switched to the other drug prior to progression.
- There are no data at this time to guide immunotherapy either before or following a tyrosine kinase inhibitor.
- There are no data on sequential tyrosine kinase inhibitors beyond second line.
- CheckMate 040 [4] is a non-comparative phase 1/2 dose escalation study and therefore not eligible for inclusion in the evidence for this guideline. However, in this trial nivolumab had a safety profile that was manageable and a promising response rate. Health Canada has approved the use of nivolumab as second-line treatment based on the response rate in this study. There is a Health Canada indication for nivolumab but it is not currently funded at present for those who are intolerant to sorafenib or who have progressed on sorafenib.
- This recommendation may need to be updated with respect to the use of ramucirumab in those with high alpha-fetoprotein levels once the REACH-2 trial data have been fully published.

Recommendation 5

- The treatment of hepatitis B virus (HBV) is recommended for patients with advanced HCC who are hepatitis B surface antigen positive as it prevents reactivation of HBV and progression of liver disease in general.
- There is no evidence for or against the eradication of hepatitis C virus (HCV) in patients with advanced HCC.

Qualifying Statements for Recommendation 5

- The data addressing the oncologic effects of treating HBV are weak and it is unlikely that there will be randomized data to address this issue in the future.
- In the Xu et al. [5] study, patients with *reactivated* HBV who received antiviral rescue therapy had significantly better survival than those who did not want rescue therapy (median OS, 23.7 months vs. 8.6 months; $p=0.023$).
- There are currently no ongoing trials to address the issue of the eradication of HCV in patients with advanced HCC.
- The evidence for the use of interferon to eradicate HCV in patients with HCC is confounded by its anti-tumour effects. It is impossible to parse out whether improvements in patients with HCC are owing to the eradication of HCV or directly owing to the anti-tumour effects.
- Interferon is no longer used to eradicate HCV. Direct-acting antivirals are now used.
- HCC patients who are HCV positive have better survival than HCC patients who are HBV positive when treated with sorafenib.
- It is unknown if there are survival differences in HCV and HBV populations when treated with TACE, TAE, or TEA.
- Patients who are HBV and/or HCV positive should be seen by a hepatologist or gastroenterologist to manage their underlying liver disease.

GLOSSARY

LOCAL THERAPIES

- RFA - radiofrequency ablation
- SBRT - stereotactic body radiation therapy
- TEA - transarterial ethanol ablation

REGIONAL THERAPIES

- cTACE - conventional transarterial chemoembolization
- DEB-TACE - drug eluting bead transarterial chemoembolization
- SIRT - selective internal radiation therapy (same as TARE)
- TAE - bland transarterial embolization
- TARE - transarterial radioembolization

DEFINITIONS (<http://www.cancer.ca/en/cancer-information/cancer-type/liver/staging/?region=qc>)

- Barcelona Clinic Liver Cancer (BCLC) Stage B (Intermediate Stage)
 - Child-Pugh A or B
 - Multifocal disease but tumours are not causing symptoms.
 - ECOG = 0
- Barcelona Clinic Liver Cancer (BCLC) Stage C (Advanced Stage)
 - Child-Pugh A or B
 - Tumour(s) have grown into blood vessels or there has been spread to other body sites. Tumour(s) are causing symptoms.
 - ECOG = 1 or 2