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CancerCare Manitoba Clinical Practice Guidelines

Provincial Consensus Recommendations on the Non-Surgical Management of Advanced Hepatocellular Carcinoma

Version 1.0 — September 29, 2023

CancerCare Manitoba Guideline
Disease Management – Hepatocellular Carcinoma
Developed by: Liver DSG

1.0 Background

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This clinical practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with the UOM departments of Hepatology, Pathology and Radiology, community and interprovincial partners. Members of the Community Oncology, Hepatology, Hepatobiliary Surgery, Medical Oncology, Pathology, Radiation Oncology, Radiology, Community Cancer Program Network, Clinical Operations, and Nurse Navigation departments have participated in its development.

The Liver Disease Site Group (DSG) will review and update this document every 3 years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the non-surgical management of advanced hepatocellular carcinoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but are not limited to): physicians, oncologists, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB, and Community Oncology Program sites (Community Cancer Program Network (CCPN) sites, Uniting Primary Care and Oncology (UPCON) clinics and Winnipeg Regional Health Authority (WRHA) Community Oncology sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of advanced hepatocellular carcinoma. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgement, nor should it replace consultation with the appropriate oncology specialist when indicated (example:

medical oncologist, radiation oncologist, family practitioner in oncology (FPO), hepatologist, nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under their care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

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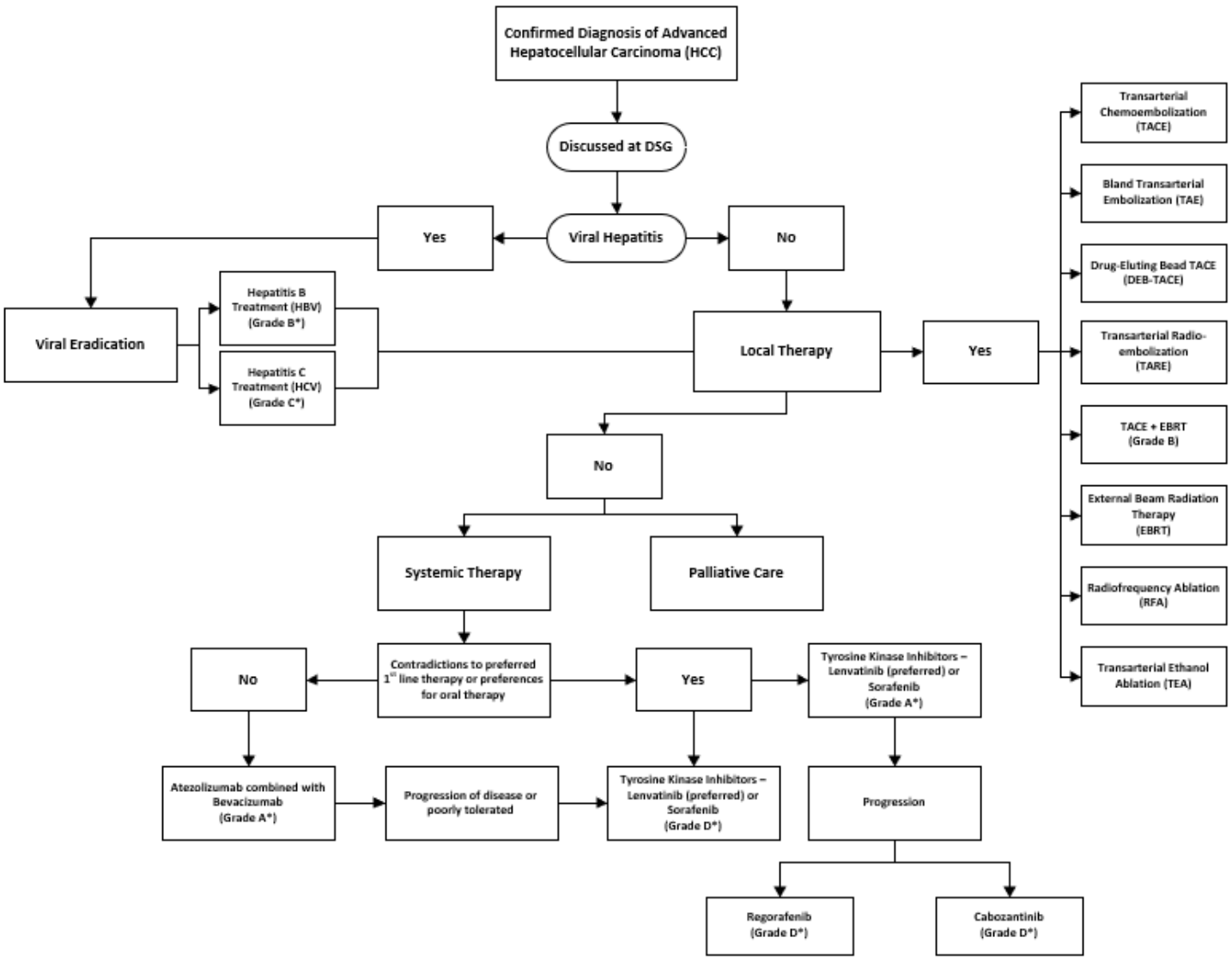
Guideline Recommendations – Flowchart



*Grade of Recommendation – see Appendix 1

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Guideline Recommendations - Summary

Treatment recommendations

(1) Transarterial Chemoembolization (TACE) vs. other Local Therapies

What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], external beam radiation therapy [EBRT] and drug eluting bead TACE [DEB-TACE] versus conventional TACE in patients with advanced HCC?

We adopt the recommendations set forth by the CancerCare Ontario Guidelines (2019). "There is insufficient evidence to recommend for or against the use of TEA, TAE, RFA, TARE, EBRT, or DEB-TACE instead of cTACE, which has been the conventional standard of care, in patients with intermediate-stage HCC or higher."

(2) Combining TACE with EBRT

What is the benefit of combining TACE with EBRT in patients with advanced HCC?

1. TACE in combination with EBRT for HCC, particularly if associated with portal vein tumour thrombus, improves overall survival (level of evidence 2++). **Grade of recommendation B.**

(3) 1st Line Systemic Therapy

What is the best 1st line systemic treatment in patients with advanced HCC?

1. Atezolizumab combined with bevacizumab should be used as first-line systemic therapy (level of evidence 1++). **Grade of recommendation A.**
2. Tyrosine kinase inhibitors such as lenvatinib (preferred – level of evidence 1+) or sorafenib (level of evidence 1++) should be used first-line in patients with contra-indications to bevacizumab & atezolizumab. **Grade of recommendation A**. These tyrosine kinase inhibitors could also be considered as first-line options for those patients who express a preference for orally administered (vs parenteral) systemic therapy.

(4) 2nd Line Systemic Therapy

What is the best 2nd line systemic treatment in patients with advanced HCC?

1. Lenvatinib (preferred) or sorafenib or may be used in the second line setting if the disease progresses or if the patient does not tolerate bevacizumab & atezolizumab. **Grade of recommendation D**.
2. If the patient had sorafenib or lenvatinib as first-line therapy, the following agents can be considered for second-line therapy: cabozantinib (if disease progressed on, or if the patient did not tolerate 1st line tyrosine kinase inhibition (level of evidence 1+) or regorafenib (if the patient tolerated but progressed on sorafenib (level of evidence 1+) **Grade of recommendation D.**

(5) Eradication of Viral Hepatitis

What is the benefit of eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

1. We adopt the recommendations set forth by the CancerCare Ontario Guidelines (2019). "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 new evidence since the above-mentioned publication. **Grade of recommendation B**.
2. Hepatitis C virus (HCV) treatment with direct acting antiviral agents (DAA) in patients with advanced HCC is controversial. Recent retrospective analysis in patients with advanced HCC suggests a survival advantage to treating with DAA therapy (level of evidence 2+). **Grade of recommendation C**.

CancerCare Manitoba
Disease Management Recommendations
Provincial Consensus Recommendations on the Non-Surgical Management of Advanced Hepatocellular Carcinoma

I. Introduction to Advanced Hepatocellular Carcinoma in Manitoba

Liver cancer is the second most common cause of cancer-related mortality and the fifth cancer in incidence worldwide.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver tumour.[2] The incidence of HCC has been rising throughout the past three decades and is anticipated to continue rising through 2032, based on modeling studies for hepatitis B virus and hepatitis C virus and the prevalence of obesity.[3] In Canada, HCC is the second fastest increasing cancer in incidence after thyroid cancers in both sexes.[4]

The 5-year relative survival rate for all HCC is 20% in Canada[5]. In Manitoba (MB) the 1, 2, 3, 4- and 5-year survival rates for patients diagnosed with HCC between 2011 and 2015 are 41%, 27%, 19%, 17%, and 14%, respectively.[6] Multi-disciplinary approach for the management of HCC is of extreme importance not only because of the degree of complexity in diagnosis and poor liver functions at diagnosis but also due to the multiple options of therapeutic interventions that could be considered for the patients.[7, 8] In addition to the Canadian Association for the Study of Liver Disease's (CASLD) report on the management of HCC[9], Alberta[10], and Saskatchewan[11] are among other Canadian provinces that have developed their own guidelines for the assessment and treatment of HCC. With the development and implementation of guidelines, patient care will be streamlined in pathways that are clear to different medical teams involved in the care of those patients.

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II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation pertinent to the current standards in practice for treatment of advanced hepatocellular carcinoma in Manitoba. The overall aim is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

This document is designed to outline the evidence and the degree of recommending the use of different non-curative/non-surgical treatment modalities for advanced HCC.

Development Panel

Development Panel	
Oncology Subspecialties CancerCare Manitoba/University of Manitoba	1 Radiation Oncologist, Liver DSG; 1 Radiation Oncology Resident 1 Medical Oncologists, Liver DSG; 1 Medical Oncology Resident 1 Family Physician in Oncology
Internal Medicine University of Manitoba	1 Hepatologist
Pathology University of Manitoba	1 Pathologist
Radiology University of Manitoba	1 Radiologist
Surgery University of Manitoba	1 Hepatobiliary Surgeon
Community Oncology Program CancerCare Manitoba	1 Clinical Operations Specialist (Industrial Engineer) 1 Nurse Navigator

Development Process

A multidisciplinary group of medical professionals organized bi-weekly meetings to establish management consensus for patients with advanced hepatocellular carcinoma. Attendees were experts and practitioners from within the province. Presentations included evidence-based recommendations, as well as local expertise. The guidelines were developed using a modified Delphi consensus method (see Section III, Guideline Methodology).

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of adult (18 years or older) patients with hepatocellular carcinoma, Barcelona Clinic Liver Cancer (BCLC) Stage B (intermediate stage) and higher, who are not suitable for transplant or surgery. These recommendations are intended for use in both inpatient and outpatient settings.

End-Users

This guideline is written for use by clinicians providing care for the above-mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, allied healthcare staff, healthcare administrators, policy makers and possibly members of the general public.

Excluded from Guideline

This guideline does not cover:

- Etiology, diagnosis or staging of HCC
- Curative therapy options for HCC
- Other non-HCC primary or secondary liver tumors

III. Guideline Methodology

Clinical Research Question Development

Prior to beginning a literature search, the working group assessed the clinical research questions from the Cancer Care Ontario (CCO) Non-Surgical Management of Advanced Hepatocellular Carcinoma guideline. [12] The clinical research questions were either adopted or adapted following the PICOT method (Population; Intervention; Comparison; Outcome; Time Frame). We updated the evidence by performing a literature review from January 2018 (6 months prior to the search end-date of the CCO literature search) and forward until December 2020. In addition, we have modified some questions, deleted and added others as detailed later in this document.

Clinical Questions
1- Transarterial Chemoembolization (TACE) vs. other Local Therapies What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], external beam radiation therapy [EBRT] and drug eluting bead TACE [DEB-TACE] versus conventional TACE in patients with advanced HCC?
2- What is the benefit of combining TACE with EBRT in patients with advanced HCC?
3- What is the best 1st line systemic treatment in patients with advanced HCC?
4- What is the best 2nd line systemic treatment in patients with advanced HCC?
5- What is the benefit of eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

Literature Search

Clinical Practice Guidelines

Guidelines were searched environmentally by the guideline developer, including Alberta Health Services (AHS), BC Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), Cancer Care Ontario (CCO), Saskatchewan Cancer Agency (SCA), National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), Belgian Health Care Knowledge Centre (KCE), Cancer Australia, European Society of Medical Oncology (ESMO), Guideline International Network (GIN), New Zealand Guidelines Group (NZGG), Scottish

Intercollegiate Guideline Network (SIGN), National Cancer Institute (NCI) at the National Institutes of Health (NIH), National Guideline Clearinghouse (NGC), National Health and Medical Research Council (NHMRC), and National Institute for Health and Care Excellence (NICE).

Literature Review of Primary Evidence

Primary evidence was searched systematically via PubMed, MEDLINE (Ovid), and EMBASE to obtain recent evidence for the clinical research questions that were not substantially addressed in existing guidelines. Separate literature reviews were completed for the clinical research questions. Combinations of the keywords used for the searches are shown in Table 1 (PubMed), Table 2 (Medline), and Table 3 (EMBASE) of Appendix 3. Identification of additional articles was completed using a snowballing technique, which involved moving backwards by following references of eligible papers and forward through citation chasing. Environmental searches of Google and Google Scholar were completed to obtain any relevant articles that were not presented on the databases but were of limited value. In order to update the existing recommendations and evidence present in the CCO Non-Surgical Management of Advanced Hepatocellular Carcinoma guideline[12], we conducted literature searches with the timeline from January 01st, 2018 to December 31st, 2020.[a]

Quality Appraisal of Relevant Guidelines

The CCO Non-Surgical Management of Advanced Hepatocellular Carcinoma guideline[12] was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II instrument).[13] This standardized instrument is used to assess the quality of the guideline based on methodological rigour and transparency of the development process. Further, the working group considered the currency of the guideline, rapidity of updates, relevance to the PICOT questions, and applicability for the Manitoba context when considering whether to adopt or adapt an existing guideline. The working group concurred with the AGREE II score as provided by the Partnership Against Cancer.[14]

Assessing Evidence and Grading Recommendations (SIGN Methodology)

The Scottish Intercollegiate Guidelines Network (SIGN) grading system was used to assess the level of evidence of key articles and grade the formulated recommendation statements. This methodology was chosen because it grades the clinical evidence and strength of recommendation using a clear and easy-to-follow format that is applicable to our project.[15] (Please see Appendix 1).

[a] Valuable clinical trials published after December 31st, 2020, are mentioned in supplementary notes – Clinical Question #1-3, Pages 28 & 29

Working Group Meetings

The working group developed this guideline in response to the Liver Disease Site Group (DSG) chair identifying a need for guidelines regarding the treatment of advanced hepatocellular carcinoma in Manitoban patients. The recently released CCO Non-Surgical Management of Advanced Hepatocellular Carcinoma guideline[12] was chosen to be adapted since it covered most of the areas that our group was interested to examine. It also provided a thorough review of evidence and balanced recommendations. Working group members drafted each of the guideline sections or made the necessary modifications to the chosen guideline to adapt. Each section was reviewed by the working group and revised according to consensus decisions.

Internal and External Review

Internal and external peer reviews were pursued, the results of which are appended to these guidelines. The internal review consisted of initial assessment by Dr. Gabor Fischer (pathologist and member of the working group), revision by the working group, and final review by the Liver DSG. An external review was conducted by Dr. Laura Dawson, PMH, Toronto, ON., and Dr. Vincent Tam, BCCA, Vancouver, BC. All participants completed a full review of the guideline document and submitted a standardized practitioner feedback survey (adapted from Brouwers and colleagues).[16] Feedback was considered and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection, or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered ‘living’ documents which require ongoing evaluation, review, and update. Re-evaluation of this guideline is planned for 2026. The working group will revise and update the document as required, with any critical new evidence brought forward before this scheduled review.

IV. Transarterial Chemoembolization (TACE) vs. other Local Therapies

Clinical Question 1

What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], external beam radiation therapy [EBRT] and drug eluting bead TACE [DEB-TACE] versus conventional TACE in patients with advanced HCC?

Background

There are multiple available locoregional therapies available for the management of unresectable hepatocellular carcinoma (HCC). The standard of care has been conventional transarterial chemoembolization (TACE). Alternative locoregional therapies include transarterial ethanol ablation (TEA), bland transarterial embolization (TAE), external beam radiotherapy (EBRT), radiofrequency ablation (RFA), transarterial radioembolization (TARE), and transarterial drug-eluting bead chemoembolization (DEB-TACE). Head-to-head comparisons of these alternative therapies to TACE as standard of care are limited, with current guidelines emphasizing that there is insufficient evidence to recommend any specific alternative to TACE in the management of intermediate and advanced stage HCC. There is likewise no strong consensus on subgroups which may benefit from alternative locoregional therapies. Specifically, the European Association for the Study of the Liver (EASL) 2018 practice guidelines recommend TACE for eligible non-resectable HCC (high level of evidence, recommendation strong).[17] The American Association for the Study of Liver Diseases (AASLD) 2018 practice guidelines do not recommend one form of locoregional therapy over another, but classify quality of evidence for TACE as moderate, with quality of evidence for TARE, EBRT, and TAE rated as very low.[18]

Clinical practice guidelines provided by the National Comprehensive Cancer Network (NCCN) recommend that inoperable tumors be considered for treatment by arterially directed therapy, EBRT, or systemic therapy but do not offer definitive guidance as to which locoregional therapy is preferable, except that EBRT be specifically considered in patients with contraindications to ablative and transarterial therapies. NCCN guidelines also emphasize that percutaneous ablative therapies are most effective for early-stage HCC and that there is likely to be only an adjunct role for RFA in the management of intermediate and advanced stage disease.[19]

CancerCare Ontario (CCO) guidelines released in 2019 specifically address TEA, TAE, EBRT, RFA, TARE, and DEB-TACE

in comparison to TACE. Based on a systematic review of the literature through July 2018, there was insufficient evidence to recommend for or against any of the locoregional alternatives to TACE standard of care. [12]

Key Evidence

TEA

There is a single randomized controlled trial (RCT) comparing TEA to TACE, terminated early for futility. There was no significant difference in overall survival (OS), time to progression (TTP), or progression free survival (PFS) between study arms. [20]

TAE

A 2017 network meta-analysis inclusive of four RCTs comparing TAE to TACE did not demonstrate any survival benefit or objective response (OR) benefit. [21] No interval high quality evidence was identified.

EBRT

Combination therapy with TACE and EBRT is discussed separately in Section VI.

No high quality RCTs were available for review comparing EBRT with TACE standard of care. Preliminary results of a Phase III trial comparing EBRT to TACE in patients with incomplete response to prior TACE identified improved local control with EBRT but no difference in OS or PFS.[22] This study has been terminated due to slow enrollment.

A network meta-analysis of the subset of HCC patients with portal vein invasion performed in 2018 did not identify any difference in disease control or OS between TACE and EBRT. This analysis was limited by indirect comparison and risk of bias in included studies as well as lack of RCT trials.[24] Subsequent to this meta-analysis, there have been three relevant propensity score analyses with inconsistent findings, but with two of the three identifying improved local control with EBRT compared to TACE.[25-27] The only analysis demonstrating OS benefit to EBRT identified significant benefit only in patients previously treated with TACE, with no difference for newly diagnosed HCC. [27]

RFA

No RCTs comparing TACE to RFA in the target population were identified. A 2017 retrospective study found no significant OS difference between study arms after propensity score analysis was applied.[28 A] 2006 retrospective single-centre study found no significant difference in TTP or OS, and a higher complication rate with RFA.[29]

TARE

A 2016 systematic review of five RCTs showed no statistically significant difference in survival for up to 4 years between the two groups.[30] A separate 2017 network meta-analysis inclusive of three RCTs comparing TARE to TACE

and one RCT comparing TARE to DEB-TACE showed no survival benefit or objective response (OR) benefit.[21] Since time of publication, preliminary results from the TRACE trial (ClinicalTrials.gov identifier: NCT01381221), an RCT in Belgium, identify improved TTP and OS with TARE when compared to DEB-TACE.[31] Other systematic reviews inclusive of both RCTs and retrospective cohort studies identify improved side effect profile with TARE versus cTACE.[32]

DEB-TACE

The most inclusive systematic analysis of RCTs published in 2020 included six RCTs comparing TACE with DEB-TACE. No significant difference in OS, treatment response, or major complications was found.[33] A 2017 meta-analysis including four of these same RCTs as well as two RCTs comparing TAE to DEB-TACE also found no significant advantages.[21]

Recommendations

We adopt the recommendations set forth by the CancerCare Ontario Guidelines (2019). "There is insufficient evidence to recommend for or against the use of TEA, TAE, RFA, TARE, EBRT, or DEB-TACE instead of conventional TACE, which has been the conventional standard of care, in patients with intermediate-stage HCC or higher." [a]

No grade of recommendation was assigned to this question since the recommendation was adopted directly from CCO Guidelines.

Qualifying Statement

Selection of locoregional therapy in qualifying patients will depend largely on Child-Pugh score, location of disease, volume of disease, and the number of lesions. Patients may be treated with TACE for some of their lesions but may also be treated with other locoregional therapies for specific other lesions. In select cases, TARE may be preferred over TACE in portal vein thrombosis because of lower risk of hepatic parenchymal damage and ischemia, as well as in lesions close to large vasculature in the liver in which TACE may have a higher complication profile. There is likely to be only an adjunct role for RFA in the management of intermediate and advanced stage disease. EBRT may be specifically considered in patients with contraindications to ablative and transarterial therapies. The decision to pursue and/or continue locoregional therapy versus systemic therapy can be challenging and should be made on a case-by-case basis at multidisciplinary rounds.

[a] Valuable clinical trials published after December 31st, 2020, are mentioned in supplementary notes – Clinical Question #1-3, Pages 28 & 29

References

1. Unresectable hepatocellular carcinoma: randomized controlled trial of transarterial ethanol ablation versus transcatheter arterial chemoembolization. [20] [Level of evidence 1+]

2. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. [21] [Level of evidence 1+]

3. Network meta-analysis of treatment regimens for inoperable advanced hepatocellular carcinoma with portal vein invasion. [24] [Level of evidence 2+]

4. Comparison of Stereotactic Body Radiation Therapy and Transarterial Chemoembolization for Unresectable Medium-Sized Hepatocellular Carcinoma.[27] [Level of evidence 2++]

5. Application of radiofrequency ablation for the treatment of intermediate-stage hepatocellular carcinoma. [28] [Level of evidence 2+]

6. Comparable survival in patients with unresectable hepatocellular carcinoma treated by radiofrequency ablation or transarterial chemoembolization.[29] [Level of evidence 2-]

7. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: A systematic review and meta-analysis.[30] [Level of evidence 1+]

8. Transarterial strategies for the treatment of unresectable hepatocellular carcinoma: A systematic review.[32] [Level of evidence 1-]

9. A comparison between drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with hepatocellular carcinoma: A meta-analysis of six randomized controlled trials.[33] [Level of evidence 1+]

VI. Combining TACE with EBRT

Clinical Question 2

What is the benefit of combining TACE with EBRT in patients with advanced HCC?

Background

Multiple treatment modalities have been employed in the management of unresectable hepatocellular carcinoma (HCC). The optimal sequencing and combination of treatments is not known; in particular the combination of transarterial chemoembolization (TACE) with external beam radiation therapy (EBRT). TACE is typically delivered directly to the tumour volume via the hepatic artery through a fluoroscopically directed catheter, with different agents used in different centres.[34] EBRT can be delivered with different techniques including 3D-conformal radiation therapy (3D-CRT) and stereotactic body radiotherapy (SBRT). Traditionally TACE is used for treatment of unresectable HCC with other therapies, including EBRT, reserved for use in patients with unresponsive or persistent HCC.

Recent advances in EBRT techniques, including the use of stereotactic body radiotherapy (SBRT, aka stereotactic ablative radiotherapy – SABR) have brought into question the role of EBRT in the current disease paradigm. From a review of the available guidelines and evidence, there is no strong consensus on the recommendations regarding the use of TACE with SBRT, as most guidelines were silent regarding combination treatment, and rather they focused more on mono-therapeutic options. Therefore, the decision was made to compose our own statement of recommendation based on the available evidence.

Key Evidence

Recent guidelines released from CancerCare Ontario in 2019 [12] did not address the particular question of EBRT use in unresectable HCC. Guidelines updated from the National Comprehensive Cancer Network (NCCN) did allow for the use of EBRT, and in particular SBRT, as "an alternative to the ablation/embolization techniques" or "when these therapies have failed or are contraindicated".[19] It stressed that most data arise from patients with Child-Pugh A (CP-A) liver disease, and that safety data is limited for those with CP-B or C disease, although it may be possible to safely deliver radiation with strict dose constraint adherence in those with CP-B disease.

Multiple retrospective reviews have been performed to evaluate the combination of EBRT and TACE. A 2019 propensity score matched analysis from Hong Kong compared patients receiving TACE to those receiving TACE and EBRT. It found in patients without portal vein thrombus and CP ≥7 that those treated with both TACE and EBRT had

a better overall and progression free survival with an acceptable side effect profile.[35] A network meta-analysis from 2017 compared TACE+RT to TACE alone amongst other combination matched treatments, found that TACE+RT was the most effective treatment strategy with better survival results and no difference in adverse events.[21] An abstract presented for interim results of an ongoing phase III trial comparing SBRT vs. TACE after an incomplete response to TACE found superior local control for SBRT with no difference in toxicity.[22]

In the setting of portal vein thrombosis (PVT), multiple reports have also been published. A network meta-analysis from Taiwan in 2018 compared TACE alone vs. EBRT combined with TACE and found for CP A&B patients, those treated with combination therapy had better disease control and overall survival.[24] A meta-analysis from Asia in 2016 compared TACE vs. TACE+RT in the setting of portal vein tumour thrombus (PVTT) and found that combination therapy showed better overall survival although there was worse grade 3-4 leukopenia and thrombocytopenia in the TACE+RT group.[36] A propensity score analysis from 2016 found that for PVT type II and III that TACE+RT showed better response and median survival compared to TACE alone with no difference in toxicity.[37]

Recommendations

TACE in combination with EBRT for HCC, particularly if associated with portal vein tumour thrombus, improves overall survival (level of evidence 2++). **Grade of recommendation B.** [a]

References

1. Better survival after stereotactic body radiation therapy following transarterial chemoembolization in non-resectable hepatocellular carcinoma: A propensity score matched analysis.[35] [Level of evidence 2++]

2. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. [21] [Level of evidence 1+]

3. Abstract ESTRO 2020: SBRT versus TAE/TACE in Hepatocellular Carcinoma: results from a Phase III trial (NCT02323360).[22]

4. Network meta-analysis of treatment regimens for inoperable advanced hepatocellular carcinoma with portal vein invasion. [24] [Level of evidence 2+]

5. Comparison of intra-arterial chemoembolization with and without radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a meta-analysis. [36] [Level of evidence 2++]

[a] Valuable clinical trials published after December 31st, 2020, are mentioned in supplementary notes – Clinical Question #1-3, Pages 28 & 29

6. Efficacy of the treatment of transarterial chemoembolization combined with radiotherapy for hepatocellular carcinoma with portal vein tumor thrombus: A propensity score analysis. [37] [Level of evidence 2++]

7. Multimodality Treatment for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Large-Scale, Multicenter, Propensity Matching Score Analysis. [38] [Level of evidence 2++]

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VII. Systemic Therapy – First Line Systemic Therapies

Clinical Question 3

What is the best 1st line systemic treatment for advanced HCC?

Background

Prior to the introduction of tyrosine kinase inhibitors into the therapeutic armamentarium for hepatocellular carcinoma, no effective systemic therapies existed for the treatment of locally advanced, unresectable HCC or for metastatic HCC. With the publication of studies such as the SHARP [40] trial in 2008, sorafenib became the standard of care in the first-line therapy for unresectable, locally advanced HCC and for metastatic HCC. The publication of the IMBrave [41] study in May 2020 represented a significant advance in the treatment of HCC, establishing the combination of the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab as the preferred first-line therapy for those patients without contraindications to these agents. An expert panel convened by the American Society for Clinical Oncology (ASCO) to conduct a systematic review of phase III randomized studies published between January 1, 2007 and May 15, 2020 produced a clinical practice guideline on the management of advanced HCC which was published in November 2020. With respect to systemic therapy options, our group takes the ASCO guideline to reflect the standard of care for advanced HCC and undertook a literature review with a view to modifying the recommendations in the ASCO document as warranted by the literature and adapting them for use in Manitoba.

Key Evidence

Studies conducted prior to 2018 which were referenced in the ASCO clinical practice guideline and which were central to the task of assigning levels of evidence to the recommendations in the CCMB document were also reviewed. Included for review in this respect were the SHARP trial [40]. Published in 2008, the SHARP trial compared sorafenib with placebo in the treatment of advanced HCC in patients who were either not candidates for, or progressed on, local therapies. Randomized and double-blinded, the trial examined 602 patients and yielded a statistically significant improvement in overall survival with sorafenib compared to placebo (10.7 mo. vs 7.9) [HR 0.69 (95% CI, 0.55 to 0.87)]. [40] Lenvatinib was established as an alternative first-line systemic therapy option on the basis of a non- inferiority trial comparing lenvatinib to sorafenib which was published in the Lancet in 2018. [43] Nevertheless, lenvatinib showed superior progression-free survival (PFS) and better toxicity profile than sorafenib.

Pivotal to our recommendations regarding the first-line therapy of HCC is the IMBrave150 study, a global, randomized, open-label study which compared the combination of atezolizumab plus bevacizumab to sorafenib in patients with advanced HCC. The intention-to-treat population included 336 patients in the atezo-bev group and 165 in the sorafenib group. The hazard ratio for death with atezolizumab–bevacizumab as compared with sorafenib was 0.58 (95% confidence interval [CI], 0.42 to 0.79; P<0.001). [41, a]

Recommendations

1. Atezolizumab combined with bevacizumab should be used as first-line systemic therapy (level of evidence 1+). **Grade of recommendation A.**
2. Tyrosine kinase inhibitors such as lenvatinib (preferred TKI – level of evidence 1+) or sorafenib (level of evidence 1++) should be used first-line in patients with contra-indications to bevacizumab & atezolizumab. **Grade of recommendation A**. These tyrosine kinase inhibitors could also be considered as first-line options for those patients who express a definite preference for orally administered (vs parenteral) systemic therapy.

References

1. Sorafenib in Advanced Hepatocellular Carcinoma [40] [Level of evidence 1++]
2. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma [41] [Level of evidence 1+]
3. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [43] [Level of evidence 1+]
4. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline[46] [Level of evidence 1+]

[a] Valuable clinical trials published after December 31st, 2020, are mentioned in supplementary notes – Clinical Question #3, Page. 29.

VIII. Systemic Therapy – Second Line Systemic Therapies

Clinical Question 4

What is the best 2nd line systemic treatment for advanced HCC?

Background

Please review section VI

Key Evidence

Studies conducted prior to 2018 which were referenced in the ASCO clinical practice guideline and which were central to the task of assigning levels of evidence to the recommendations in the CCMB document were also reviewed. There is currently no level 1 evidence for second-line systemic therapy after first-line immunotherapy, but it is reasonable to consider a tyrosine kinase inhibitor such as lenvatinib (preferred) or sorafenib based on expert opinion. Three studies are key to the recommendations regarding the use of second-line tyrosine kinase inhibitors after progression on or intolerance of first-line tyrosine kinase inhibitors. Published July 15, 2018 in the NEJM, the CELESTIAL trial [44] was a randomized, double-blind, phase 3 trial which evaluated cabozantinib as compared with placebo in previously treated patients with advanced hepatocellular carcinoma. Median overall survival was 10.2 months with cabozantinib and 8.0 months with placebo (hazard ratio for death, 0.76; 95% confidence interval [CI], 0.63 to 0.92; P=0.005). REACH-2 [45] was a randomized, double-blind, placebo-controlled, phase 3 trial examining the role of ramucirumab as second-line therapy for HCC that had progressed on first-line sorafenib in the sub-population of HCC patients whose serum alpha-fetoprotein levels exceeded 400 ng/mL (HR, 0.67; 95% CI, 0.51 to 0.90). Nevertheless, Ramucirumab has not been approved yet by pan-Canadian Oncology Drug Review (pCODR). RESORCE (vide supra) compared the use of regorafenib to placebo in the second-line therapy of patients who tolerated but progressed on first-line sorafenib. Regorafenib improved overall survival with a hazard ratio of 0·63 (95% CI 0·50–0·79; one-sided p<0·0001). [42]

Recommendations

1. Lenvatinib (preferred) or Sorafenib may be used in the second line setting if the disease progresses or if the patient does not tolerate bevacizumab & atezolizumab. **Grade of recommendation D**.

2. If the patient had sorafenib or lenvatinib as first-line therapy, the following agents can be considered for second-line therapy: cabozantinib (if disease progressed on, or if the patient did not tolerate 1st line tyrosine kinase inhibition (level of evidence 1+) or regorafenib (if the patient tolerated but progressed on sorafenib (level of evidence 1+) **Grade of recommendation D**.

References

1. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial [42] [Level of evidence 1+]

2. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma [44] [Level of evidence 1+].

Qualifying Statements

Recent cost-benefit analyses suggest that the financial cost of immune checkpoint inhibitor (ICI) monotherapy as second-line systemic treatment for HCC might exceed user willingness to pay. For example, the current cost per quality-adjusted life year (QUALY) for pembrolizumab is ~ CDN$250,000.[47] Currently, single-agent ICIs such as pembrolizumab or nivolumab should not be considered as options for 2nd line therapy (see Qualifying Statements, below) but their potential role should be re-evaluated as the evidence evolves regarding their efficacy, safety, and cost-benefit ratio in this setting.

IX. Viral Hepatitis (HCV and/or HBV)

Clinical Question 5

What is the benefit of eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

Background

The treatment of hepatitis B virus (HBV) with antiviral therapy is recommended for patients with advanced HCC as it minimizes reactivation risk with systemic therapy, TACE, or EBRT. There is also the possibility for lower risk of progression of HCC with antiviral therapy. On the other hand, the benefit to treatment of hepatitis C virus (HCV) using direct acting antiviral agents (DAA) remains unclear in advanced HCC, due to a lack of data as these patients were excluded from studies. There exists the theoretical concern that treatment with DAA therapy has the potential to accelerate tumor progression in advanced HCC although this has not been shown in more recent studies. There also is reduced success of HCV eradication with antiviral therapy in patients with HCC as they tend to have a lower sustained virological response rate (SVR). On the other hand, DAA therapy may improve liver function and ultimately prolong survival in these patients. Current American Association for the Study of Liver Disease (AASLD) guidelines recommend consideration for DAA therapy in patients with expected survival exceeding 1 year. If this is true, with increasing survival of patients with advanced HCC owing to more effective systemic therapy, there exists a need to better understand which patients would benefit from DAA therapy as the competing importance of maintaining stable liver function plays a greater role.

Key Evidence

We were tasked to review existent CancerCare Ontario Guidelines (2019)[12] with regards to treatment of hepatitis B and/or C in the setting of advanced HCC as defined by Barcelona B or greater HCC not amenable to surgical intervention. These guidelines stipulate that 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. The guidelines could not make any firm recommendations for or against eradication of hepatitis C virus (HCV) in patients with advanced HCC. A literature search conducted between January 1, 2018 and December 1, 2020 yielded 47 abstracts of which 8 publications were ultimately identified and reviewed. Our search did not yield new evidence to challenge the existent guidelines of treating all hepatitis B patients with advanced HCC with the goal of preventing Hepatitis B reactivation. [49]

Eradication of hepatitis C in all patients with advanced HCC is more controversial but there were a few studies worth mentioning since the Ontario Guidelines were published. For example, there is suggestion of improved patient

survival among patients receiving palliative treatment for HCC with a median survival for the SVR group being approximately 8 months longer than those of untreated patients (27.39 months versus 19.66 months). [50]

With respect to the concern over lack of efficacy of oral DAA therapy in HCV eradication in patients with advanced HCC, a prospective cohort study recently published suggest similar treatment efficacy to non-HCC patients and with acceptable safety profile. [51]

Perhaps the most important new data came from Kamp et al who provided a retrospective analysis of a subgroup of HCC patients that were not surgical candidates and who received ablation therapy, transcatheter tumor therapy (TACE or TARE) or combination therapy. Those receiving DAA therapy, and in particular those who achieved SVR had a nearly 3-fold increase in medium survival as compared with those who were not offered therapy. There were likely to have been inherent bias in this study due to its retrospective nature and heterogeneous tumor burden.[52, 53] A survey at 47 tertiary care centers in the US published in Clinical Hepatology and Gastroenterology affirms present views that there exists variation in practice patterns among prescribers of DAA treatment in patients with HCC and more studies are needed to direct therapy.[54]

Finally, as immune check point inhibitors are increasingly being considered for therapy in advanced HCC patients with concomitant hepatitis B and/or C, a systematic review of the literature suggest these to be safe to use and that antiviral therapy in these patients should be considered when deemed appropriate.[55]

Recommendations

We adopt the recommendations set forth by the CancerCare Ontario Guidelines (2019). “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 new evidence since the above-mentioned publication. **Grade of recommendation B**.

Hepatitis C virus (HCV) treatment with direct acting antiviral agents (DAA) in patients with advanced HCC is controversial. Recent retrospective analysis in patients with advanced HCC suggests a survival advantage to treating with DAA therapy (level of evidence 2+). **Grade of recommendation C**.

References

1. Nucleos(t)ide analogues and Hepatitis B virus-related hepatocellular carcinoma: A literature review. [49] [Level of evidence 3]

2. Cure with Interferon-Free Direct-Acting Antiviral Is Associated with Increased Survival in Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma from Both East and West.[50] [Level of evidence 2-]

3. Equal treatment efficacy of direct-acting antivirals in patients with chronic hepatitis C and hepatocellular carcinoma? A prospective cohort study.[51] [Level of evidence 2-]

4. Direct-Acting Antivirals Improve Overall Survival in Interventional Oncology Patients with Hepatitis C and Hepatocellular Carcinoma. [52] [Level of evidence 2+]

5. Impact of Direct Acting Antivirals on Survival in Patients with Chronic Hepatitis C and Hepatocellular Carcinoma.[53] [Level of evidence 2+]

6. Safety and efficacy of immune checkpoint inhibitors in patients with HBV/HCV infection and advanced-stage cancer: A systematic review. [54] Level of evidence 2++]

7. Provider Attitudes and Practice Patterns for Direct-Acting Antiviral Therapy for Patients with Hepatocellular Carcinoma. [55] [Level of evidence 4]

Qualifying Statements

Direct acting antiviral (DAA) therapy in patients with hepatitis C virus (HCV) and advanced HCC undergoing radiofrequency ablation (RFA), image guided transcatheter tumor therapy (TACE or TARE) or combination therapy may be associated with an increase in median survival likely owing to improved liver function and should be used when deemed appropriate.[52]

Treatment with Direct acting antiviral (DAA) in patients with hepatitis C virus (HCV) and advanced HCC undergoing systemic therapy is controversial and requires more study. However, as our success and expected patient survival increases with these agents, there likely will be a benefit to treat.

The timing of treatment with Direct acting antiviral (DAA) therapy in patients with hepatitis C virus (HCV) and advanced HCC requires further research as data is lacking.

Antiviral therapy in patients with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) should be considered when deemed appropriate in patients with advanced HCC being treated with immune check point inhibitors (ICI).

X. Supplementary Notes

General Recommendations

Treatment decisions should be made on a case-by-case basis in multidisciplinary rounds aimed at achieving consensus management strategy.

Clinical trials should be encouraged wherever appropriate and available.

Notes on Clinical Question 1

What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], external beam radiation therapy [EBRT] and drug eluting bead TACE [DEB-TACE] versus conventional TACE in patients with advanced HCC?

-Evidence is accumulating from clinical trials (that were published after this guideline was internally reviewed) to suggest that SBRT might produce a better clinical outcome when compared to TACE. TRENDY Phase II trial randomized patients with HCC to receive either TACE-DEB or SRBT. SRBT showed higher local antitumoral activity than TACE-DEB, without detrimental effects on OS, toxicity and QoL. [60] In addition, NCT00857805 trial randomized patients with untreated HCC, meeting Milan or San Francisco transplant criteria, to receive either radiation with proton beam therapy (PBT) or TACE. PBT and TACE yielded similar OS, but PFS and LC were improved with PBT compared to TACE. [61]

Notes on Clinical Question 2

What is the benefit of combining TACE with EBRT in patients with advanced HCC?

-Evidence from NCT02323360 phase III clinical trial (published after this guideline was internally reviewed) showed that SBRT was an effective treatment option in patients affected by inoperable HCC experiencing an incomplete response following 1 cycle of TAE/TACE. In this trial, patients were randomized to SBRT versus standard TAE/TACE for the curative treatment of the intermediate stage of HCC after an incomplete response to TAE/TACE. SBRT showed a statistically significant improvement in LC compared to TAE/TACE. [62]

Notes on Clinical Question 3

What is the best 1st line systemic treatment for advanced HCC?

-In Checkmate 459, in which 743 patients with HCC were randomized to nivolumab (n = 371) or sorafenib (n =372) with a minimum follow-up of 22.8 months at data cut-off, OS did not meet the predefined threshold of statistical significance (HR 0.84, P ¼ 0.0419). However, median OS (mOS) was 16.4 months for nivolumab and 14.7 months for sorafenib (HR 0.85 [95% CI: 0.72–1.02]; P ¼ 0.0752). Clinical benefit was observed across predefined subgroups, including hepatitis infection status, presence of vascular invasion and/or extrahepatic spread, and region (Asia vs non-Asia). [48]

-Phase III HIMALAYA trial showed that a single priming dose of tremelimumab added to durvalumab led to a statistically significant improvement in survival as compared to sorafenib in first line. The combination of tremelimumab with durvalumab may be considered as an alternative to Atezulizumzb/Bevacizumab.[59] This trial was not published by the time the guideline was internally approved by the specialists therefore it was added to the supplementary notes.

Notes on Clinical Question 4

What is the best 2nd line systemic treatment for advanced HCC?

-A specific recommendation has not been made with respect to the role of hepatic arterial infusion of chemotherapy (HIAC) in the treatment of unresectable HCC or HCC that progresses on treatment. HAIC is widely employed in Asian countries in the management of HCC. Numerous studies have failed to demonstrate a benefit with cytotoxic HAIC such as with doxorubicin or platinum-based HIAC.[56] However, several recent studies purport to show a benefit with HAIC, and particularly with HAIC plus sorafenib over sorafenib alone in the treatment of advanced HCC. For example, a recent study retrieved in this literature review demonstrates a statistically significant effect of HIAC with FOLFOX.[57] In that study, published in JAMA in July 2019, for 247 patients (median age, 49 years; range, 18-75 years), median overall survival was 13.37 months (95% CI, 10.27-16.46) in the SoraHAIC group vs 7.13 months (95% CI, 6.28-7.98) in the sorafenib group (hazard ratio [HR], 0.35; 95% CI, 0.26-0.48; P < .001).

-There are studies pertinent to the role of immune checkpoint inhibition underway which may change the landscape of the treatment of HCC in the future, including the RATIONALE 301 study and the Nivolumab With or Without Ipilimumab in Treating Patients With Resectable Liver Cancer study (ClinicalTrials.gov, NCT03222076). [58] These are yet to be proven strategies and will not be addressed in the current guidelines, but will need to be assessed when the evidence is more robust.

- Considering the new recommendation for 1st line use of atezolizumab-bevacizumab, and as an extrapolation of level 1+ evidence for the 2nd line use of cabozantinib or regorafenib after 1st line tyrosine kinase inhibition, these agents can be considered for 3rd line use after 1st line atezolizumab-bevacizumab followed by 2nd line sorafenib or lenvatinib.

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XII. Implementation and Dissemination

The value of guidelines lies within their implementation and use. For that purpose, consideration was given to implementation during the drafting of this guideline document. Several tools emerged:

CancerCare Resources

It was recognized that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels: the Community Oncology Program to CCPN rural sites, UPCON clinics, and WRHA Community Oncology Program sites. This guideline will also be provided to partner organizations and guidelines reviewers in other provinces. Use of the guideline in clinics will be through the online version.

Educational Events

Presentation of the guideline's recommendations will be made available at rounds and conferences: Liver DSG rounds, CCMB Haematology/Oncology Regional Grand rounds, Allied Health rounds (Patient Services rounds), CCPN Community Cancer Care annual educational conference, UPCON education and training events and at other events.

Training

The members of the HCC working group will utilize the guideline for the purpose of staff training (physicians, allied health) at CancerCare Manitoba, University of Manitoba, and wherever deemed required.

XIII. Concordance Measurement

A plan is being developed regarding the guideline concordance measurement and will be presented to the CCMB standards committee for approval. Briefly, a panel will review randomly selected cases at CCMB and provide a confidential feedback form covering the key recommendations to the treating physicians/surgeons. Suggestions will be presented in an encouraging format. The audit and feedback process will be done under the auspices of the CCMB standards committee, and include the protections therein. A formal comprehensive chart-based audit to assist adherence to the guidelines document will be planned for all newly diagnosed HCC cases.

XIV. Contact Physicians and Contributors

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XV. Conflict of Interest

In accordance with the CCMB policy no. 01.001, “Conflict of Interest”, the authors of this guideline disclosed no conflicts of interest and declares that no commercial support was received during the development of this guideline

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XVI. Appendices

Appendix 1

SIGN Grading System (1999-2012)

Levels of Evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or

	Extrapolated evidence from studies rated as 2+

Good Practice Points

✓	Recommended best practice based on the clinical experience of the guideline development group

Health Improvement Scotland. SIGN Grading System 1999-2012. https://www.sign.ac.uk/assets/sign_grading_system_1999_2012.pdf

Appendix 2

Literature Search Methodology

Table 1. Literature Review Search Terms – PubMed

Clinical Research Question	Search Strategy
TACE vs. other Local Therapies	"hepatocellular carcinoma" AND "chemoembolization, therapeutic" AND ("embolization, therapeutic" OR "stereotactic radiation" OR "radiofrequency ablation" OR "radioisotope therapy") Filters: 2018/08/01–2020/12/31, English language, Human species **Note:** Of the 111 results, 11 were subject to an in-depth review.
Combining TACE with EBRT	((hepatocellular carcinoma) AND (chemoembolization)) AND (stereotactic radiotherapy) Filters: 2016/01/01–2020/12/31, English language **Note:** Of the 72 results, 7 were subject to an in-depth review.
1st and 2nd line Systemic Treatments	(((hepatocellular carcinoma [MeSH Major Topic]) OR (hepatocellular cancer [MeSH Major Topic])) AND (drug therapy [MeSH Terms]) OR (immunotherapy [MeSH Terms])) Exclusion criteria: hearing [Title], pancreatic [Title], breast [Title], colorectal [Title], lung [Title] Filters: Clinical Trial, Clinical Trial Phase III, Clinical Trial Phase IV, Meta-Analysis, 2018/1/1–2020/12/31, English language, Human species **Note:** 105 articles resulted.
Eradication of Viral Hepatitis	(((((((hepatitis B [MeSH Terms]) OR (hepatitis b, chronic [MeSH Terms])) OR (HBV [MeSH Terms])) OR (hepatitis C [MeSH Terms])) OR (hepatitis c, chronic [MeSH Terms])) OR (HCV [MeSH Terms]))) AND (agents, antiviral [MeSH Terms])) AND (hepatocellular carcinoma [MeSH Major Topic]) Filters: 2018/1/1–2020/12/31, English language, Human species **Note:** 374 articles resulted.

Table 2. Literature Review Search Terms – MEDLINE

Clinical Research Question	Search Strategy
TACE vs. other Local Therapies	1. Carcinoma, Hepatocellular/ 2. ((hepatocellular or liver) adj3 (cancer* or carcinoma*)).mp. 3. hepatoma*.mp. 4. 1 or 2 or 3 5. Chemoembolization, Therapeutic/ 6. (trans* adj3 chemoembolization).mp. 7. 5 or 6 8. 4 and 7 9. limit 8 to (english language and humans and yr="2018 - 2020") **Note:** 989 articles resulted <u>Each comparison was then addressed separately:</u> 10. TEA.mp. 11. Transarterial ethanol ablation.mp. 12. 10 or 11 13. 9 and 12 **Note:** 0 articles resulted 14. Bland transarterial embolization.mp. 15. Transarterial bland embolization.mp. 16. Bland embolization.mp. 17. TAE.mp. 18. 14 or 15 or 16 or 17 19. 9 and 18 **Note:** Of the 30 results, 2 additional articles from Medline were subject to an in-depth review. 20. SBRT.mp. 21. Stereotactic body radiation therapy.mp. 22. SART.mp. 23. Selective ablative radiation therapy.mp.

	24. 20 or 21 or 22 or 23 25. 9 and 24 **Note:** Of the 33 results, 4 additional articles from Medline were subject to an in-depth review. 26. Radiofrequency ablation.mp. 27. RFA.mp. 28. 26 or 27 29. 9 and 28 **Note:** Of the 153 results, 2 additional articles from Medline were subject to an in-depth review. 30. TARE.mp. 31. Transarterial radioembolization.mp. 32. Yttrium.mp. 33. Selective internal radiation therapy.mp. 34. Selective internal radiation treatment.mp. 35. 30 or 31 or 32 or 33 or 34 36. 9 and 35 **Note:** Of the 64 results, 7 additional articles from Medline were subject to an in-depth review. 37. Drug eluting bead$.mp. 38. DEB-TACE.mp. 39. 37 or 38 40. 9 and 39 **Note:** Of the 84 results, 12 additional articles from Medline were subject to an in-depth review.
Combining TACE with EBRT	1. Carcinoma, Hepatocellular/ 2. ((hepatocellular or liver) adj3 (cancer* or carcinoma*)).mp. 3. hepatoma*.mp. 4. 1 or 2 or 3 5. radiosurgery/ or radiotherapy, conformal/ or radiotherapy, intensity-modulated/ or radiotherapy, image-guided/ 6. Chemoembolization, Therapeutic/

	7. ((radiotherapy or radiation) adj3 stereotactic).mp. 8. (trans* adj3 chemoembolization).mp. 9. 5 or 6 or 7 or 8 10. 4 and 9 11. limit 10 to (yr="2016 - 2020" and english and "therapy" and medline) **Note:** Of the 156 results, 1 additional article from Medline was subject to an in-depth review.
1st and 2nd line Systemic Treatments	1. Carcinoma, Hepatocellular/ 2. hepatocellular ADJ3 (cancer* OR neoplasm* OR carcinoma*).mp. 3. 1 or 2 4. drug therapy/ or antineoplastic protocols/ or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or induction chemotherapy/ or maintenance chemotherapy/ or molecular targeted therapy 5. Immunotherapy/ 6. bevacizumab/ or ipilimumab/ or nivolumab 7. ((PD-1 OR PD-L1 OR CTLA-4) adj1 (inhibitor* OR block*)). ti, ab, kf, tw. 8. pembrolizumab.ti,ab, kf,tw. 9. atezolizumab.ti,ab,kf,tw. 10. durvalumab.ti,ab,kf,tw. 11. avelumab.ti,ab,kf,tw. 12. tremelimumab.ti,ab,kf,tw. 13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. 3 and 13 15. limit 14 to yr=”2018-2020” 16. limit 15 to (english and (clinical trial, phase iii or meta-analysis)) 17. ("phase 3" or "phase III").ti,ab,kf,tw. 18. 15 and 17 19. meta-analysis.ti,ab,kf,tw. 20. 15 and 19 21. 18 or 20 22. limit 21 to English language

	Note: Of the 78 results, 19 additional articles from Medline were subject to an in-depth review.
Eradication of Viral Hepatitis	1. Carcinoma, Hepatocellular/ 2. ((hepatocellular or liver) adj2 (cancer* or carcinoma*)).mp. 3. hepatoma*.mp. 4. 1 or 2 or 3 5. hepatitis B/ or HBV/ or hepatitis C/ or HCV/ 6. antiviral*.mp. 7. 4 and 5 and 6 8. limit 7 to (yr="2018 - 2020" and english)

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Table 3. Literature Review Search Terms – EMBASE

Clinical Research Question	Search Strategy
TACE vs. other Local Therapies	1. Carcinoma, Hepatocellular/ 2. ((hepatocellular or liver) adj3 (cancer* or carcinoma*)).mp. 3. hepatoma*.mp. 4. 1 or 2 or 3 5. Chemoembolization, Therapeutic/ 6. (trans* adj3 chemoembolization).mp. 7. 5 or 6 8. 4 and 7 9. limit 8 to (human and english language and "therapy (maximizes sensitivity)" and yr="2018 - 2020") **Note:** 1515 articles resulted <u>Each comparison was then addressed separately:</u> 10. TEA.mp. 11. Transarterial ethanol ablation.mp. 12. 10 or 11 13. 9 and 12 **Note:** Of the 4 results, 0 additional articles from EMBASE were subject to an in-depth review. 14. Bland transarterial embolization.mp. 15. Transarterial bland embolization.mp. 16. Bland embolization.mp. 17. TAE.mp. 18. 14 or 15 or 16 or 17 19. 9 and 18 **Note:** Of the 34 results, 0 additional articles from EMBASE were subject to an in-depth review. 20. SBRT.mp. 21. Stereotactic body radiation therapy.mp.

	22. SART.mp. 23. Selective ablative radiation therapy.mp. 24. 20 or 21 or 22 or 23 25. 9 and 24 **Note:** Of the 105 results, 6 additional articles from EMBASE were subject to an in-depth review. 26. Radiofrequency ablation.mp. 27. RFA.mp. 28. 26 or 27 29. 9 and 28 **Note:** Of the 373 results, 1 additional article from EMBASE were subject to an in-depth review. 30. TARE.mp. 31. Transarterial radioembolization.mp. 32. Yttrium.mp. 33. Selective internal radiation therapy.mp. 34. Selective internal radiation treatment.mp. 35. 30 or 31 or 32 or 33 or 34 36. 9 and 35 **Note:** Of the 140 results, 9 additional articles from EMBASE were subject to an in-depth review. 37. Drug eluting beads.mp. 38. DEB-TACE.mp. 39. 37 or 38 40. 9 and 39 **Note:** Of the 122 results, 12 additional articles from EMBASE were subject to an in-depth review. **Note:** The snowball technique retrieved additional 0 studies for in depth review. **Note:** A TOTAL OF 66 STUDIES SELECTED FOR FULL REVIEW.

Combining TACE with EBRT	1. liver cell carcinoma/ 2. ((hepatocellular or liver) adj3 (cancer* or carcinoma*)).mp. 3. hepatoma*.mp. 4. 1 or 2 or 3 5. radiotherapy/ or beam therapy/ or external beam radiotherapy/ or image guided radiotherapy/ or intensity modulated radiation therapy/ or photon therapy/ or stereotactic body radiation therapy/ or stereotactic radiosurgery/ or volumetric modulated arc therapy/ 6. chemoembolization/ 7. ((radiotherapy or radiation) adj3 stereotactic).mp. 8. (trans* adj3 chemoembolization).mp. 9. 5 or 6 or 7 or 8 10. 4 and 9 11. limit 10 to (embase and "therapy (best balance of sensitivity and specificity)" and english and yr="2016 - 2020") **Note:** Of the 408 results, no additional articles from EMBASE were subject to an in-depth review.
1st and 2nd line Systemic Treatments	1. liver cell carcinoma/ 2. hepatocellular adj3 (cancer* or neoplasm* or carcinoma*).mp. 3. 1 or 2 4. drug therapy/ 5. immunotherapy/ 6. ((PD-1 or PD-L1 or CTLA-4) adj1 (inhibitor* or block*)).mp. 7. pembrolizumab.mp. 8. atezolizumab.mp. 9. durvalumab.mp. 10. avelumab.mp. 11. tremelimumab.mp. 12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. 3 and 12 14. limit 13 to (english language and meta-analysis and (clinical trial or phase 3 clinical trial or phase 4 clinical trial))

	15. ("Phase 3" or "Phase III" or "Phase 4" or "Phase IV").mp. 16. 14 and 15 17. meta-analysis.mp. 18. 14 and 17 19. 16 or 18 20. limit 19 to yr="2018-2020" **Note:** 30 articles resulted.
Eradication of Viral Hepatitis	**Note:** The Cochrane, TRIP, and Scopus databases were used instead of searching EMBASE. For this clinical question, a total of 47 abstracts were identified across all databases; 39 were discarded due to irrelevant information and 8 publications were assessed in-depth.

Appendix 3

Internal Review

This has been completed in September 2023.

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CCMB Clinical Practice Guideline: Disease Management
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