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PRACTICE GUIDELINE

Nonsurgical management of advanced hepatocellular carcinoma: a clinical practice guideline

B.M. Meyers MSc MD,*[a] J. Knox MD,†[a] R. Cosby MA,‡ J.R. Beecroft MD,§ K.K.W. Chan MD,‖ N. Coburn MD MPH,‖ J. Feld MD,# D. Jonker MD,** A. Mahmud MD,†† J. Ringash MD,†‡‡ and the Gastrointestinal Disease Site Group

ABSTRACT

Background Practice guidelines based on a systematic review of the literature regarding the nonsurgical management of hepatocellular carcinoma (HCC) in North America are lacking. Resection and transplantation are the foundations for cure of HCC; however, most patients are diagnosed at an advanced stage, precluding those curative treatments. A number of local or regional therapies are used and are followed by systemic therapy for advanced or progressive disease. Other treatments are available, but their efficacy, compared with those standards, is not well known.

Methods First, systematic review questions were developed. Literature searches of the MEDLINE, EMBASE, and Cochrane library databases (January 2000 to July 2018 or January 2005 to July 2018 depending on the question) were conducted; in addition, abstracts from the 2018 annual meeting of the American Society of Clinical Oncology were reviewed. A practice guideline was drafted that was then scrutinized by internal and external reviewers.

Results Seventy-seven studies were included in the guideline: no guidelines, two systematic reviews, and seventy-five primary studies published in full (including one pooled analysis). Five recommendations were developed.

Conclusions There is no evidence for or against the use of local or regional interventions other than transarterial chemoembolization for the treatment of intermediate- or advanced-stage HCC. Furthermore, there is no evidence to support the addition of sorafenib to any local or regional therapy. Sorafenib or lenvatinib are recommended for first-line systemic treatment of intermediate-stage HCC. Regorafenib or cabozantinib provide survival benefits when given as second-line treatment. Antiviral treatment is recommended in individuals with advanced HCC who are positive for the hepatitis B surface antigen.

Key Words Nonsurgical treatments, hepatocellular carcinoma, practice guidelines, systemic therapy, tyrosine kinase inhibitors

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INTRODUCTION

Between 1984 and 2011, the incidence of liver cancer increased steadily in Canadian men and women[1]. Specifically, the incidence increased annually by 3.8% in men and by 2.7% in women. That rising incidence might be attributable partly to immigration from regions in which exposure to risk factors for liver cancer such as hepatitis B (HBV), hepatitis C (HCV), and aflatoxin are much more common[1]. The mortality from liver cancer has also been steadily increasing. Since the mid-1990s, mortality has increased annually by 3.1% in men and by 2.2% in women in Canada[1].

Hepatocellular carcinoma (HCC) accounts for approximately 72% of all primary liver cancers in Canada. This disease is a global health problem, accounting for 4.7% of all new cancer cases and 8.2% of all cancer deaths worldwide in 2018[2]. In Ontario in 2019, an estimated 1170 new incident cases of liver cancer were expected to be diagnosed (39.3% of the estimated new incident liver cancer cases in Canada),

[a] These authors contributed equally to this guideline.

Correspondence to: Brandon Meyers, Department of Oncology, McMaster University, Juravinski Campus, 699 Concession Street, Hamilton, Ontario L8V 5C2. E-mail: meyersbr@hhsc.ca **DOI:** https://doi.org/10.3747/co.27.5891

and 550 deaths from liver cancer were expected to occur (39.9% of the estimated liver cancer deaths in Canada)[1]. The predicted 5-year net survival for liver cancer during 2012–2014 was 19% [95% confidence interval (CI): 18% to 20%] for men and women combined[1].

Resection and transplantation are the foundational therapies for HCC cure; however, most patients are diagnosed at an advanced stage, precluding those curative treatments. The current standard of practice for the treatment of advanced HCC varies with hospital and local expertise. Furthermore, head-to-head comparisons of those techniques have been limited. Noncurative treatments include transarterial chemoembolization (TACE) and, in the case of advanced disease, systemic therapies such as sorafenib. Other treatments are available, but compared with TACE and sorafenib, their efficacy rates are not well known. The purpose of the present guideline was to review the current evidence for all treatment options in advanced unresectable HCC to help standardize care across Ontario.

RESEARCH QUESTIONS

This guidance document examined the evidence to answer these questions about the treatment of patients with locally advanced or advanced HCC (Barcelona Clinic Liver Cancer stage B or higher):

1. What are benefits of other local therapies—transarterial ethanol ablation (TEA), bland transarterial embolization (TAE), radiofrequency ablation (RFA), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), and drug-eluting bead transarterial chemoembolization (DEB-TACE)—compared with TACE?
2. What is the benefit of the addition of sorafenib to local therapies (TEA, TAE, RFA, TARE, SBRT, TACE, DEB-TACE)?
3. What is the benefit of other systemic treatment regimens compared with sorafenib?
4. What is the benefit of the eradication of viral hepatitis (HCV or HBV, or both) in patients with advanced HCC?
5. What is the benefit of second-line systemic therapy after sorafenib?
6. Is there a survival difference in populations having HCV compared with populations having HBV and compared with populations not affected by those viruses when treated with sorafenib?
7. Is there a survival difference in populations having HCV compared with populations having HBV and compared with populations not affected by those viruses when treated with TACE, TAE, or TEA?

METHODS

The Gastrointestinal Disease Site Group (DSG) of the Program in Evidence-Based Care (PEBC) at Ontario Health (Cancer Care Ontario) developed this guideline. The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[3,4]. That process includes a systematic review, interpretation of the evidence and drafting of recommendations by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

Search for Existing Guidelines

As a first step in developing the present guideline, a search for existing evidence-based guidelines (that is, based on a systematic review) was undertaken to determine if an existing guideline could be adapted or endorsed. To that end, these sources were searched for existing guidelines addressing the research questions: MEDLINE, EMBASE, the U.S. Agency for Healthcare Research and Quality, the U.S. National Guideline Clearinghouse, the Canadian Medical Association Infobase, the U.K. National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, the American Society of Clinical Oncology (ASCO), and Australia's National Health and Medical Research Council. Guidelines considered relevant to the research questions were then evaluated for quality using the AGREE II framework[5]. The 23-item validated AGREE II tool is designed to assess the methodologic rigour and transparency of guideline development.

Search for Systematic Reviews

The search for existing systematic reviews was undertaken in these databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the ASCO library of meeting abstracts. Identified systematic reviews were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of the present guideline. Systematic reviews that were found to be directly relevant—and therefore a potential foundation for our evidence review—were assessed using the AMSTAR tool[6].

Search for Primary Literature

A relevant systematic review was available for the TARE compared with TACE part of question 1 and one relevant systematic review was available for question 6. A search for primary studies was undertaken in MEDLINE and EMBASE from the time at which the latter systematic review ended up to July 2018. The newer relevant primary studies are included for question 6. No relevant systematic review was available for any other comparison in question 1 or for any other question. A search for primary studies was therefore undertaken.

If more than one publication was available for any given trial, only the most recent publication was included. Randomized controlled trials were assessed using the Cochrane Risk of Bias tool and all studies that were not randomized controlled trials were assessed using the Risk of Bias in Non-Randomized Studies of Interventions tool.

Literature Search Strategy

The MEDLINE and EMBASE databases were searched from 2000 to July 2018 for question 1 and from 2005 to July 2018 for questions 2–7. In addition, abstracts from the ASCO 2018 annual meeting were searched for relevant studies. Reference lists from included studies were also searched. Specific search strategies for each question are available upon request to the corresponding author.

Data Extraction

Data from the included systematic review and primary studies were extracted by one member of the Working Group (RC). All extracted data and information were subsequently audited by an independent auditor.

Internal Review

Guidelines prepared by the PEBC are reviewed by a panel of content experts (the Expert Panel) and a methodology panel (the Report Approval Panel). Both panels must approve the document. The Working Group was responsible for incorporating the feedback and required changes received from both panels.

External Review

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

RESULTS

Literature Search Results

Guidelines

The guideline search sought guidelines published in 2013 and later. Practice guideline databases and guideline developer Web sites did not yield any relevant guidelines. The MEDLINE and EMBASE searches yielded 7987 total "hits," of which 388 publications underwent full-text review; none were considered suitable for endorsement or adaptation.

Systematic Reviews

A search for systematic reviews uncovered 5423 documents, of which 374 underwent full-text review. Two were retained[7,8].

Primary Studies

The literature search returned 37,645 "hits," of which 863 publications underwent a full-text review, with 71 being retained. Two ASCO abstracts and two studies found by searching reference lists of the included studies were also retained, for a total of seventy-five primary studies[9–83]. Also included in the search was one pooled analysis, which was retained. Table I summarizes all the studies included in the evidence base for the guideline.

Internal Review

Expert Panel Review and Approval

The Gastrointestinal DSG acted as the Expert Panel for the present guideline. To approve a guideline document, 75% of the Gastrointestinal DSG membership must cast a vote or abstain, and of the members who vote, 75% must approve the document. Of the 27 eligible members of the Gastrointestinal DSG, 22 cast votes and 0 abstained, for a total response rate of 81.5%. Of the 22 members who cast votes, all approved the document (100%).

Report Approval Panel Review and Approval

The guideline was reviewed in August 2018 by 3 Report Approval Panel members. The Report Approval Panel approved the document on 20 August 2018.

External Review

Targeted Peer Review

The Working Group identified 4 targeted peer reviewers from Ontario, California, and Massachusetts who are considered to be clinical or methodology experts on the topics being addressed. Two agreed to be reviewers. Two responses were received.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, radiation oncologists, and surgical oncologists with an interest in gastrointestinal cancers in the PEBC database were contacted by e-mail to inform them of the survey. In addition, interventional radiologists from Ontario and hepatologists from across Canada were identified and asked to participate. Of 140 potential respondents identified, 17 (12%) responded to the survey.

GUIDELINE

Recommendation 1

The evidence for or against improved survival with 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 or greater HCC, is insufficient. Decisions about treatment should be made on a case-by-case basis. Each case should be evaluated separately at a multidisciplinary cancer conference that includes medical oncologists, radiation oncologists, surgical oncologists, hepatologists, and interventional radiologists. Short-term follow-up data indicate that toxicity might be less with TARE than with TACE, but longer-term follow-up data are not available.

Qualifying Statements for Recommendation 1

In the management of intermediate-stage or greater HCC, treatment decisions depend largely on Child–Pugh score, location of disease, volume of disease, and number of lesions.

Typically, patients with early-stage disease not amenable to surgery could be treated with RFA or one of the other local or regional therapies. If that treatment fails, they could be treated with TACE for some lesions, but also with other local or regional therapies for other specific lesions.

Failure to benefit from prior local or regional therapies should trigger early consideration of systemic treatment. In addition, recent abstract data from the large international OPTIMIS study[84] showed an improvement in overall survival (OS) for patients starting early on sorafenib therapy upon assessment of standard TACE ineligibility compared with patients receiving no sorafenib at that time. The same study also demonstrated that, in a real-world experience,

TABLE I Studies selected for inclusion

Question	Publications retained		References
	Systematic reviews	Primary literature	
1 Local therapy compared with TACE			
TEA compared with TACE	0	1	9
TAE compared with TACE	0	4	10–13
RFA compared with TACE	0	2	14,15
TARE compared with TACE	1	2	8,16,17
SBRT compared with TACE	0	0	—
DEB-TACE compared with TACE	0	4	18–21
Other	0	0	—
2 Local therapy plus sorafenib compared with local therapy			
TEA plus sorafenib compared with TEA	0	0	—
TAE plus sorafenib compared with TAE	0	0	—
RFA plus sorafenib compared with RFA	0	1	22
TARE plus sorafenib compared with TARE	0	2	23,23
SBRT plus sorafenib compared with SBRT	0	0	—
TACE plus sorafenib compared with TACE	0	4	25–28
DEB-TACE plus sorafenib compared with DEB-TACE	0	2	29,30
Other	0	0	—
3 Sorafenib compared with other systemic therapy	0	23	31–53
4 Eradication of hepatitisC or B virus	0	8	54–61
5 Second-line systemic therapy after sorafenib	0	20	62–18
6 Survival difference in hepatitisC or B virus after sorafenib	1	1[a]	7,82
7 Survival difference in hepatitisC or B virus after TACE, TAE, or TEA	0	1	83

[a] Pooled analysis.

TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation; TAE = bland transarterial embolization; RFA = radiofrequency ablation; TARE = transarterial radioembolization; SBRT = stereotactic body radiation therapy; DEB-TACE = drug-eluting bead transarterial chemoembolization.

deviation from treatment guidelines for TACE and not starting sorafenib (systemic therapy) are common and detrimental. In addition, patient selection for TACE is extremely important. Comorbidities, liver function (beyond Childs–Pugh A), and patient performance status (for example, by the Eastern Cooperative Oncology Group method) have to be thoroughly assessed.

The decision to stop TACE (if ineffective or if serious toxicity is experienced) and to move on to systemic therapy can be challenging and should be made on a case-by-case basis at an multidisciplinary cancer conference. Treating patients who are TACE-unresponsive or TACE-ineligible might make them ineligible to benefit from systemic therapy.

Further randomized data are required to make more definitive statements about the use of local or regional therapies compared with TACE.

Key Evidence for Recommendation 1

Overall, head-to-head comparisons of the various local therapies with TACE are generally small and of moderate-to-poor quality.

Recommendation 2

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

Qualifying Statement for Recommendation 2

After failure of local therapies, suitable patients should be considered for treatment with systemic therapy.

Key Evidence for Recommendation 2

The evidence for the addition of sorafenib to local or regional therapies is either nonexistent (TEA, TAE, and SBRT) or negative.

No randomized data for the addition of sorafenib to TARE exist. Retrospective[23] and case–control[24] studies are small and contradictory.

Survival was not affected by the addition of sorafenib to conventional TACE ($p = 0.790$)[25].

Survival was not affected by the addition of sorafenib to DEB-TACE in both the SPACE trial [hazard ratio (HR): 0.898; 95% CI: 0.606 to 1.330; $p = 0.295$][29] and the TACE 2 trial (HR: 0.91; 95% CI: 0.67 to 1.24; $p = 0.57$)[30].

Recommendation 3

For first-line single-agent systemic therapy, two tyrosine kinase inhibitors (sorafenib and lenvatinib) are currently recommended as having 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 patient inclusion criteria were stricter in the lenvatinib trial[31] than in the SHARP sorafenib trial[85] with respect to performance status (Eastern Cooperative Oncology Group 0–1 in the lenvatinib trial vs. 0–2 in the SHARP trial) and additional exclusions in the lenvatinib trial (one or more of Vp4 main portal vein invasion, >50% liver occupation, or invasion of the bile duct).

Because 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, a switch to the other drug could be made before progression.

A phase III trial of nivolumab compared with sorafenib (CheckMate 459) is ongoing; recommendation 3 should be revisited once the data from that trial are available.

Key Evidence for Recommendation 3

Kudo *et al.*[31] demonstrated that lenvatinib is noninferior to sorafenib with respect to survival (HR: 0.92; 95% CI: 0.79 to 1.06). Test criteria for superiority of lenvatinib over sorafenib were not met.

The SHARP trial demonstrated that, compared with placebo, sorafenib is associated with longer median OS (HR: 0.69; 95% CI: 0.55 to 0.87; $p < 0.001$)[85].

Recommendation 4

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

Qualifying Statements for Recommendation 4

The modest survival benefit associated with tyrosine kinase inhibitors has to be weighed against the side effects incurred.

For second-line therapy, the cabozantinib trial included patients who did not tolerate sorafenib; in contrast, patients in the regorafenib trial were required to tolerate a minimum sorafenib dose of 400 mg for 21 or more days in the preceding 28 days. None of the second-line trials specifically address lenvatinib; however, for patients who progress on lenvatinib, either second-line agent is reasonable.

Because 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, a switch to the other drug before progression is a possibility. That approach is based on extrapolation from other tumour sites where tyrosine kinase inhibitors are used, because no sequencing data are available. Furthermore, the first-line standard (that is, sorafenib) is more historical, but it should not preclude second-line therapy.

No data to guide immunotherapy either before or after a tyrosine kinase inhibitor are currently available.

Being a noncomparative phase I/II dose-escalation study, CheckMate 040[86] is not eligible for inclusion in the evidence for the present guideline. However, in the CheckMate 040 trial, nivolumab had a safety profile that was manageable and that was associated with a promising response rate. Health Canada approved the use of nivolumab in the second line based on the response rate in that study. A Health Canada indication for nivolumab for those who are intolerant to sorafenib or who have progressed on sorafenib is not currently funded.

Recommendation 4 might have to be updated with respect to the use of ramucirumab in patients with high levels of alpha-fetoprotein once the REACH-2 trial data have been fully published.

Key Evidence for Recommendation 4

Compared with placebo and best supportive care, regorafenib combined with best supportive care was associated with significantly better survival in the RESORCE trial (HR: 0.63; 95% CI: 0.50 to 0.79; $p < 0.0001$)[62].

Compared with placebo, cabozantinib was associated with significantly better survival in the CELESTIAL trial (HR: 0.76; 95% CI: 0.63 to 0.92; $p = 0.005$)[63].

Recommendation 5

Treatment for HBV is recommended in patients with advanced HCC who are positive for the hepatitis B surface antigen, because treatment prevents reactivation of HBV and progression of liver disease in general.

There is no evidence for or against the eradication of 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 randomized data to address this issue will be generated in the future.

In the study by Xu *et al.*[54], patients with *reactivated* HBV who received antiviral rescue therapy experienced significantly better survival than did those who did not want rescue therapy (median OS: 23.7 months vs. 8.6 months; $p = 0.023$).

Currently, no ongoing trials are addressing 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 interferon's antitumour effects. It is impossible to parse out whether improvements in patients with HCC are attributable to the eradication of HCV or directly to antitumour effects.

Interferon is no longer used to eradicate HCV. Direct-acting antivirals are now used.

When treated with sorafenib, patients with HCC who are HCV-positive experience better survival than do those who are HBV-positive.

Whether survival differences are evident in HCV- and HBV-affected populations when treated with TACE, TAE, or TEA is unknown.

Patients who are HBV- or HCV-positive (or both) should be seen by a hepatologist or gastroenterologist to manage the underlying liver disease.

Key Evidence for Recommendation 5

In the Xu *et al.*[54] study, survival was significantly better in patients with HBV who were receiving antiviral treatment in addition to sorafenib than in those receiving sorafenib alone (16.47 months vs. 13.10 months, $p = 0.03$).

Three studies[55–57] demonstrated that survival was significantly better in patients receiving HBV antiviral treatment in addition to TACE than in those receiving TACE alone.

CONCLUSIONS

There is no evidence for or against the use of local or regional interventions other than TACE for the treatment of intermediate-stage or greater HCC. Furthermore, there is no evidence to support the addition of sorafenib to any local or regional therapy. Single-agent sorafenib or lenvatinib is recommended for the first-line systemic treatment of intermediate-stage HCC. Regorafenib or cabozantinib provides a survival benefit when given as second-line treatment after progression on sorafenib. Eradication of HBV is recommended in patients with advanced HCC.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: BMM has received $5000 or more in a single year to act in a consulting capacity for Eisai and has received $5000 or more in a single year for other financial support from SillaJen. He has provided expert testimony to the pan-Canadian Oncology Drug Review for Eisai. JK has received research grants from Merck, AstraZeneca, and Pfizer to support investigator-initiated trials led by JK. She was a principal investigator for an AstraZeneca trial in adjuvant therapy for HCC (EMERALD-2). JRB is a site principal investigator for the STOP HCC trial of TARE plus sorafenib compared with sorafenib alone, which has completed recruiting. NC receives salary support as Ontario Health (Cancer Care Ontario)'s clinical lead for Patient Reported Outcomes and Symptom Management. JF has received consulting fees from AbbVie and is an advisory board member for AbbVie. He has received research grants from AbbVie, Gilead Sciences, Janssen, and Fujifilm Wako Pure Chemical, and has been a principal investigator for a trial of serum biomarkers for the detection of HCC for Fujifilm Wako Pure Chemical. All other authors declare that they have no conflicts of interest to disclose.

AUTHOR AFFILIATIONS

*Juravinski Cancer Centre, Department of Oncology, McMaster University, Hamilton; †Princess Margaret Cancer Centre, Toronto; ‡Program in Evidence-Based Care, Department of Oncology, McMaster University, Hamilton; §Department of Medical Imaging, Mount Sinai Hospital, and University Health Network, Toronto; ‖Sunnybrook Odette Cancer Centre, Toronto; #Toronto General Hospital Research Institute, Toronto; **The Ottawa Hospital Cancer Centre, Ottawa; ††Cancer Centre of Southeastern Ontario, Kingston; and ‡‡Department of Radiation Oncology, University of Toronto, Toronto, ON.

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