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Guideline 2-30a

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

Regional Therapies for Colorectal Cancer Liver Metastases

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An assessment conducted in January 2023 deferred the review of Guideline 2-30a. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 2-30a is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/63286

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Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To make recommendations regarding regional therapies for adults with resectable or unresectable liver metastases from colorectal cancer (CRC) with an emphasis on overall survival, progression-free survival, time to progression, time to hepatic progression, overall response rate, and toxicity.

TARGET POPULATION

These recommendations apply to adults with resectable or unresectable liver metastases from CRC.

INTENDED USERS

The intended users of this guideline are clinicians involved in the delivery of care to patients with liver metastases from CRC.

RECOMMENDATIONS

Recommendation 1
There was no evidence that met the stated inclusion criteria, to inform for or against the addition of cTACE, DEB-TACE, or TARE to systemic therapy for the treatment of resectable CRC liver metastases. These interventions are not recommended outside of a clinical trial.

Recommendation 2
There is insufficient evidence to recommend the addition of cTACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases outside of a clinical trial.

Recommendation 3
There is insufficient evidence to recommend the addition of DEB-TACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases outside of a clinical trial.

Recommendation 4
The addition of TARE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases is not recommended.

Recommendation 5
There was no evidence that met the stated inclusion criteria, to inform for or against the addition of cTACE, with or without systemic therapy, in the second-line (or later) treatment of unresectable CRC liver metastases. This intervention is not recommended outside of a clinical trial.

Recommendation 6
There is insufficient evidence to recommend the *routine* addition of DEB-TACE, with or without systemic therapy, in the second-line (or later) treatment of those with unresectable CRC liver metastases outside of a clinical trial. However, given that there is weak evidence for the addition of DEB-TACE, few other treatment options and low toxicity associated with DEB-TACE, consideration of this treatment and decisions regarding this treatment should be made on a case-by-case basis preferably at a multidisciplinary case conference.

Recommendation 7
There is insufficient evidence to recommend the routine addition of TARE, with or without systemic therapy, in the second-line (or later) treatment of those with unresectable CRC liver metastases outside of a clinical trial. However, given that there is weak evidence for the addition of TARE, few other treatment options and low toxicity associated with TARE, consideration of this treatment and decisions regarding this treatment should be made on a case-by-case basis preferably at a multidisciplinary case conference.

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Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations regarding regional therapies for adults with resectable or unresectable liver metastases from colorectal cancer (CRC) with an emphasis on overall survival (OS), progression-free survival (PFS), time to progression (TTP), time to hepatic progression (THP), overall response rate (ORR), and toxicity.

TARGET POPULATION

These recommendations apply to adults with resectable or unresectable liver metastases from CRC.

INTENDED USERS

The intended users of this guideline are clinicians involved in the delivery of care to patients with liver metastases from CRC.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
There was no evidence that met the stated inclusion criteria, to inform for or against the addition of cTACE, DEB-TACE, or TARE to systemic therapy for the treatment of resectable CRC liver metastases. These interventions are not recommended outside of a clinical trial.

Recommendation 2
There is insufficient evidence to recommend the addition of cTACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases outside of a clinical trial.
Key Evidence for Recommendation 2
• One retrospective four-arm study [1] was identified. This study had a moderate risk of bias as measured by ROBINS-I. Median OS, five-year PFS, and conversion to resectability were significantly better in the study arms that included cTACE along with systemic therapy.
Interpretation of Evidence for Recommendation 2
• There was agreement among the Working Group members that there was insufficient evidence regarding the addition of cTACE to systemic therapy based on the fact that the only data available came from a single retrospective study with a moderate risk of bias. Although in this study the benefits outweighed the harms, the certainty of the evidence was considered to be very low. • The Working Group was unanimous in their opinion that other key stakeholders (patients and providers) would agree with this recommendation. Patient input was subsequently sought after the recommendations were drafted through the Program in Evidence-Based Care (PEBC) patient representative consultation group and provider input was subsequently sought during the external review process (see Section 5). • The evidence regarding the addition of cTACE to systemic therapy is generalizable to the entire unresectable target population.

Recommendation 3
There is insufficient evidence to recommend the addition of DEB-TACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases outside of a clinical trial.
Key Evidence for Recommendation 3
• One small phase II randomized controlled trial (RCT) was identified [2]. This study had a high risk of bias. The main outcome was response rate and there were no significant differences between the study arms in a blinded review at two, four, and six months using RECIST 1.1. There were also no significant differences between the study arms with respect to PFS, downsizing to resection, and rates of grade 3/4 adverse events.
Interpretation of Evidence for Recommendation 3
• There was agreement among the Working Group members that there was insufficient evidence regarding the addition of DEB-TACE to systemic therapy based on the fact that the only data available came from a single small trial with a high risk of bias. In this study the benefits did not outweigh the harms and the certainty of the evidence was considered to be low. • The Working Group was unanimous in their opinion that other key stakeholders (patients and providers) would agree with this recommendation. Patient input was subsequently sought after the recommendations were drafted through the PEBC patient representative consultation group and provider input was subsequently sought during the external review process (see Section 5). • The evidence regarding the addition of DEB-TACE to systemic therapy is generalizable to the entire unresectable target population.

Recommendation 4
The addition of TARE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases is not recommended.
Key Evidence for Recommendation 4
• Three phase III RCTs (FOXFIRE, SIRFLOX, FOXFIRE-Global) that were purposively designed a priori to be pooled using individual patient data for the analysis of OS [3] were identified. These studies had a low risk of bias. OS was not significantly different in the folinic acid/fluorouracil/oxaliplatin (FOLFOX) and FOLFOX + TARE arms (p=0.61). Similarly, PFS was not significantly different in the two study arms.
Interpretation of Evidence for Recommendation 4
• There was agreement among the Working Group members that the evidence regarding this recommendation is of high quality and high certainty. The desirable effect of increased survival with the addition of TARE did not occur. The undesirable side effects were moderate. The benefits of the addition of TARE did not outweigh the risks. • Although the Working Group looked at survival, local control, quality of life, and toxicity, OS was considered to be the most important outcome. The Working Group was unanimous in their opinion that patients would also value the importance placed on survival although patient input was not sought. • The Working Group was unanimous in their opinion that other key stakeholders (patients and providers) would agree with this recommendation. Patient input was subsequently sought after the recommendations were drafted through the PEBC patient representative consultation group and provider input was subsequently sought during the external review process (see Section 5). • The evidence regarding the addition of TARE to systemic therapy is generalizable to the entire unresectable target population.

Recommendation 5
There was no evidence that met the stated inclusion criteria, to inform for or against the addition of cTACE, with or without systemic therapy, in the second-line (or later) treatment of unresectable CRC liver metastases. This intervention is not recommended outside of a clinical trial.

Recommendation 6

There is insufficient evidence to recommend the *routine* addition of DEB-TACE, with or without systemic therapy, in the second-line (or later) treatment of those with unresectable CRC liver metastases outside of a clinical trial. However, given that there is weak evidence for the addition of DEB-TACE, few other treatment options and low toxicity associated with DEB-TACE, consideration of this treatment and decisions regarding this treatment should be made on a case-by-case basis preferably at a multidisciplinary case conference.

Key Evidence for Recommendation 6

- Only one small phase III RCT of 74 participants comparing DEB-TACE using irinotecan (DEBIRI) to folinic acid/fluorouracil/irinotecan (FOLFIRI) was identified [4]. This study had an unclear risk of bias. OS, PFS, and ORR all favoured the DEBIRI arm.
- Additionally, two small single-arm phase II trials were identified [5,6]. This type of study design is not intended to be used to guide clinical decision making. This type of study is intended to be used to guide future research efforts.

Interpretation of Evidence for Recommendation 6

- There was agreement among the Working Group members that there was insufficient evidence regarding the *routine* use of DEB-TACE compared to systemic therapy based on the fact that the only data available came from one very small RCT and two single-arm studies. Although the benefits of DEBIRI outweighed the harms, the certainty of the evidence was considered to be low.
- However, whenever there is weak evidence for a treatment, few other treatment options and low toxicity for the given treatment then consideration of that treatment should be made on a case-by-case basis at a multidisciplinary case conference.
- The Working Group was unanimous in their opinion that other key stakeholders (patients and providers) would agree with this recommendation. Patient input was subsequently sought after the recommendations were drafted through the PEBC patient representative consultation group and provider input was subsequently sought during the external review process (see Section 5).
- The evidence regarding the addition of DEB-TACE, with or without systemic therapy, in second-line or greater treatment is generalizable to the entire unresectable target population.

Recommendation 7
There is insufficient evidence to recommend the routine addition of TARE, with or without systemic therapy, in the second-line (or later) treatment of those with unresectable CRC liver metastases outside of a clinical trial. However, given that there is weak evidence for the addition of TARE, few other treatment options and low toxicity associated with TARE, consideration of this treatment and decisions regarding this treatment should be made on a case-by-case basis preferably at a multidisciplinary case conference.
Key Evidence for Recommendation 7
• Only one very small phase III RCT of 46 participants was identified [7]. An additional three small retrospective studies were also identified [8-10]. • The risk of bias in this group of studies was considerable. Whereas Bester et al. [8] has a moderate risk of bias, both Hendlisz et al. [7] and Seidensticker et al. [10] were evaluated as having a high risk of bias. Even more problematic, the risk of bias of the Lawal et al. [9] study could not be determined owing to a lack of information provided in the paper. • In two studies the control arm was systemic therapy [7,9] and the addition of TARE offered no statistically significant survival advantage. • In the other two studies [8,10], the control arm was best supportive care (BSC). In these two studies, the addition of TARE resulted in a statistically significant survival advantage.
Interpretation of Evidence for Recommendation 7
• There was agreement among the Working Group members that there was insufficient evidence regarding the use of TARE, with or without systemic therapy, compared to systemic therapy or BSC based on the fact that the only data available came from one very small RCT and three small retrospective studies all with risk of bias difficulties. The desirable effects (OS) were small and the undesirable effects (toxicity) were unknown. Moreover, the certainty of the evidence was considered to be very low. • The Working Group was unanimous in their opinion that other key stakeholders (patients and providers) would agree with this recommendation. Patient input was subsequently sought after the recommendations were drafted through the PEBC patient representative consultation group and provider input was subsequently sought during the external review process (see Section 5). • The evidence regarding the addition of TARE, with or without systemic therapy, in second-line or greater treatment is generalizable to the entire unresectable target population.

IMPLEMENTATION CONSIDERATIONS

There are no implementation considerations.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-30b: Hepatic Arterial Infusion for Colorectal Liver Metastases (under development)
- PEBC Evidence-based Series #17-7: *Liver Resection for Colorectal Metastases* (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2236)

GLOSSARY

Regional Therapies

- cTACE – conventional transarterial chemoembolization
- DEB-TACE – drug-eluting bead transarterial chemoembolization
    - DEBIRI - DEB-TACE using irinotecan
- TARE - transarterial radioembolization

Outcome Terms

- ORR – overall response rate – the proportion of participants who achieve either a complete or partial response to treatment.
- OS – overall survival – the time from randomization to death (any cause).
- PFS – progression-free survival – the time from randomization to tumour progression or death (any cause).
- THP – time to hepatic progression – time from start of treatment to progression of disease in the liver.
- TTLP – time to liver progression – time from randomization to progression of disease in the liver.
- TTP – time to progression – time from randomization to disease progression

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Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The PEBC is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario) (OH [CCO]). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

This topic was identified by the Gastrointestinal Disease Site Group (GI DSG) based on a current gap in guidance on this topic and current variations in practice. Also, TARE and DEB-TACE are currently not widely available in Ontario. A separate companion guideline, which is currently under development, will address hepatic arterial infusion (HAI), which is another regional therapy for CRC liver metastases.

GUIDELINE DEVELOPERS

This guideline was developed by the GI DSG (Appendix 1). The project was led by a small Working Group of the GI DSG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in surgical oncology, interventional radiology, radiation oncology, medical oncology, and health research methodology. Other members of the GI DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all DSG members and guideline reviewers are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [11,12]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [13] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.
- General databases: MEDLINE and EMBASE

The guideline search included guidelines published in 2014 and later. Practice guideline databases and guideline developer websites did not yield any relevant guidelines. The MEDLINE and EMBASE searches yielded 607 hits in total of which 52 underwent full-text review. None were considered suitable for endorsement or adaptation. The guideline search strategy can be found in Appendix 3. A summary of these results of the guideline search can be found in Figure 4-1.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Three cancer patient survivors participated as Consultation Group members for the Regional Therapies for Colorectal Cancer Liver Metastases Working Group. They were volunteers from the OH (CCO) Patient and Family Advisory Committee (PFAC). They reviewed the draft recommendations and provided feedback on the comprehensibility, appropriateness, and feasibility of the recommendations to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration in finalizing the recommendations.

ACKNOWLEDGEMENTS

The GI DSG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sean Cleary, Laura Dawson, Laurie Elit, Howard Lim, David Liu, Sheila McNair, Jonathan Sussman, Emily Vella, for providing feedback on draft versions.
- Jillian Sing for conducting a data audit.
- Sara Miller for copy editing.

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Section 4: Systematic Review

INTRODUCTION

CRC is the third most common type of cancer among Canadian males and females, accounting for 12.9% and 10.9% of predicted cancers among males and females, respectively, in Canada in 2019 [14]. Incidence rates have decreased overall beginning in the mid-1980s through the mid-1990s. At this time it stabilized for a short time and then began to decrease again by 2000. This decrease in incidence was likely owing to the presence of CRC screening being put in place throughout Canada. This disease is a global health problem. Globally, in 2018 CRC accounted for 10.9% and 9.5% of the estimated incidence cases of cancer in males and females, respectively [15]. In Ontario in 2019, there will be an estimated 9100 new incident cases of CRC (10.4% of the estimated new-incident cancer cases in Ontario) and 3150 deaths from CRC (10.6% of the estimated cancer deaths in Ontario) [14]. The most common site of metastases in CRC is the liver. Liver metastases are the most common cause of death in adults with CRC [16].

Resection is the foundation for cure for CRC liver metastases; however, only approximately 20% of patients are suitable for surgery when liver metastases are diagnosed [17]. Those suitable would be considered for resection or local therapies prior to being considered for regional therapies. Non-curative treatment is usually systemic chemotherapy. For patients with liver-only or liver-predominant metastases that are unresectable, regional therapies may be considered, including cTACE, DEB-TACE, TARE, which is also known as selective internal radiation therapy, and HAI. The purpose of this guideline is to review the current evidence for regional therapies, except HAI, for CRC liver metastases. HAI is reviewed in a separate PEBC guideline.

The Working Group of the Colorectal Cancer Liver Metastases Guideline Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

This guidance document examined the evidence to answer the following questions:

1) What is the benefit of the addition of cTACE to systemic therapy in those with resectable CRC liver metastases?

2) What is the benefit of the addition of DEB-TACE to systemic therapy in those with resectable CRC liver metastases?

3) What is the benefit of the addition of TARE to systemic therapy in those with resectable CRC liver metastases?

4) What is the benefit of the addition of cTACE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?

5) What is the benefit of the addition of DEB-TACE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?

6) What is the benefit of the addition of TARE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?

7) What is the benefit of cTACE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

8) What is the benefit of DEB-TACE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

9) What is the benefit of TARE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews.

- Databases searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews
- Years covered for Q1,4,7 (cTACE questions) was 1990 to present
- Years covered for all other questions (DEB-TACE and TARE questions) was 2010 to present
- Search terms: See Appendix 3
- Selection criteria: English language systematic review that covered any of the current guideline questions.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 16-item AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) [18] tool to determine whether or not existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

No relevant systematic review was available for any of the guideline questions. Therefore, a search for primary studies was undertaken. If more than one publication was available for a given trial only the most recent publication was included.

Literature Search Strategy

Please see Appendix 3 for the primary literature search strategy.

Study Selection Criteria and Process

Question 1 - What is the benefit of the addition of cTACE to systemic therapy in those with resectable CRC liver metastases?
Question 2 - What is the benefit of the addition of DEB-TACE to systemic therapy in those with resectable CRC liver metastases?
Question 3 – What is the benefit of the addition of TARE to systemic therapy in those with resectable CRC liver metastases?

Inclusion Criteria
- English language
- Adults with resectable CRC liver metastases
- Includes a comparison of interest
    - cTACE + systemic therapy versus systemic therapy alone
    - DEB-TACE + systemic therapy versus. systemic therapy alone
    - TARE + systemic therapy versus systemic therapy alone
- Includes at least one outcome of interest (OS, disease-free survival [DFS], TTP, PFS, toxicity/safety)
- RCTs (if available). If RCTs not available or if only weak positive RCTs available, other comparative studies will be retained followed by single-arm phase II studies.
- N=30 minimally
- Years included:
    - cTACE questions - ≥2000
    - DEB-TACE questions - ≥2010
    - TARE questions - ≥2010

Exclusion Criteria
- Case studies, commentaries, editorials

Question 4 - What is the benefit of the addition of cTACE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?
Question 5 - What is the benefit of the addition of DEB-TACE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?
Question 6 – What is the benefit of the addition of TARE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?

Inclusion Criteria
- English language
- Adults with unresectable CRC liver metastases, first-line treatment
    - Unresectable metastases would be based on hepato-pancreatico-biliary (HPB) surgeon assessment preferably after a multidisciplinary review
    - Liver-dominant disease means limited extrahepatic metastases based on HPB surgeon assessment preferably after multidisciplinary review
- Includes a comparison of interest
    - cTACE + systemic therapy versus systemic therapy alone
    - DEB-TACE + systemic therapy versus systemic therapy alone
    - TARE + systemic therapy versus systemic therapy alone
- Includes at least one outcome of interest (OS, DFS, TTP, PFS, liver-specific PFS toxicity/safety, downsizing for resection)

- RCTs (if available). If RCTs not available or if only weak positive RCTs available, other comparative studies will be retained followed by single-arm phase II studies.
- N=30 minimally
- Years included:
    - cTACE questions - ≥2000
    - DEB-TACE questions - ≥2010
    - TARE questions - ≥2010

Exclusion Criteria
- Case studies, commentaries, editorials

Question 7 - What is the benefit of cTACE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?
Question 8 - What is the benefit of DEB-TACE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?
Question 9 – What is the benefit of TARE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

Inclusion Criteria
- English language
- Adults with unresectable CRC liver metastases, second-line (or later) treatment
    - Unresectable metastases would be based on HPB surgeon assessment preferably after discussion at a multidisciplinary review
    - Liver-dominant disease means limited extrahepatic metastases based on HPB surgeon assessment preferably after a multidisciplinary review
- Includes a comparison of interest
    - cTACE ± systemic therapy versus systemic therapy alone or BSC alone
    - DEB-TACE ± systemic therapy versus systemic therapy alone or BSC alone
    - TARE ± systemic therapy versus systemic therapy alone or BSC alone
- Includes at least one outcome of interest (OS, DFS, TTP, PFS, liver-specific PFS toxicity/safety, downsizing for resection)
- RCTs (if available). If RCTs not available or if only weak positive RCTs available, other comparative studies will be retained followed by single-arm phase II studies.
- N=30 minimally
- Years included:
    - cTACE questions - ≥2000
    - DEB-TACE questions - ≥2010
    - TARE questions - ≥2010

Exclusion Criteria
- Case studies, commentaries, editorials

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (RC). For items that warranted full-text review, one reviewer (RC) reviewed each item independently If there was any question regarding the eligibility of a given study Working Group leads (PK, RB) were consulted.

Data Extraction and Assessment of Study Quality and Potential for Bias

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

RCTs were assessed for quality and potential bias using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) and all non-RCTs were assessed using the Cochrane Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/).

Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that the outcome was better in the intervention group compared to the control group.

Synthesizing the Evidence

Meta-analysis was not planned even when more than one study was retained for a particular guideline question. Specifically, in Question 6 an individual patient data pooled analysis was already available and in Question 9 there was methodological heterogeneity among the included studies.

Oncology interventions that are not drug based are more challenging to interpret and develop recommendations about because there is often insufficient evidence regarding them. If there is strong evidence for or against a particular intervention then there is no difficulty in providing a recommendation. The challenge occurs when there is weak evidence for an intervention, there are few other treatment options available, and the intervention has low toxicity relative to benefit. In such cases there is not enough evidence to make a recommendation for the *routine* use of the intervention. However, the intervention should not be dismissed entirely either. These are situations in which the Working Group has indicated that a decision regarding the particular intervention should be made on a case-by-case basis at a multidisciplinary case conference.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews uncovered 1939 documents. Of these, 101 underwent full-text review and none were retained (Figure 4-1).

Search for Primary Literature

A search for primary literature was conducted for all questions.

Literature Search Results

For the individual study literature search there were 1554 hits. Of these, 226 underwent a full-text review and 15 [1-10,19-23] were retained. Included in this search was one relevant pooled analysis that was retained. For a summary of the full literature search results (including guidelines and systematic reviews), please refer to Figure 4-1, which is a flow diagram depicting the inclusion and exclusion of all studies for this guidance document. A summary of all included studies can be found in Table 4-1.

Figure 4-1. Literature search results flow diagram.

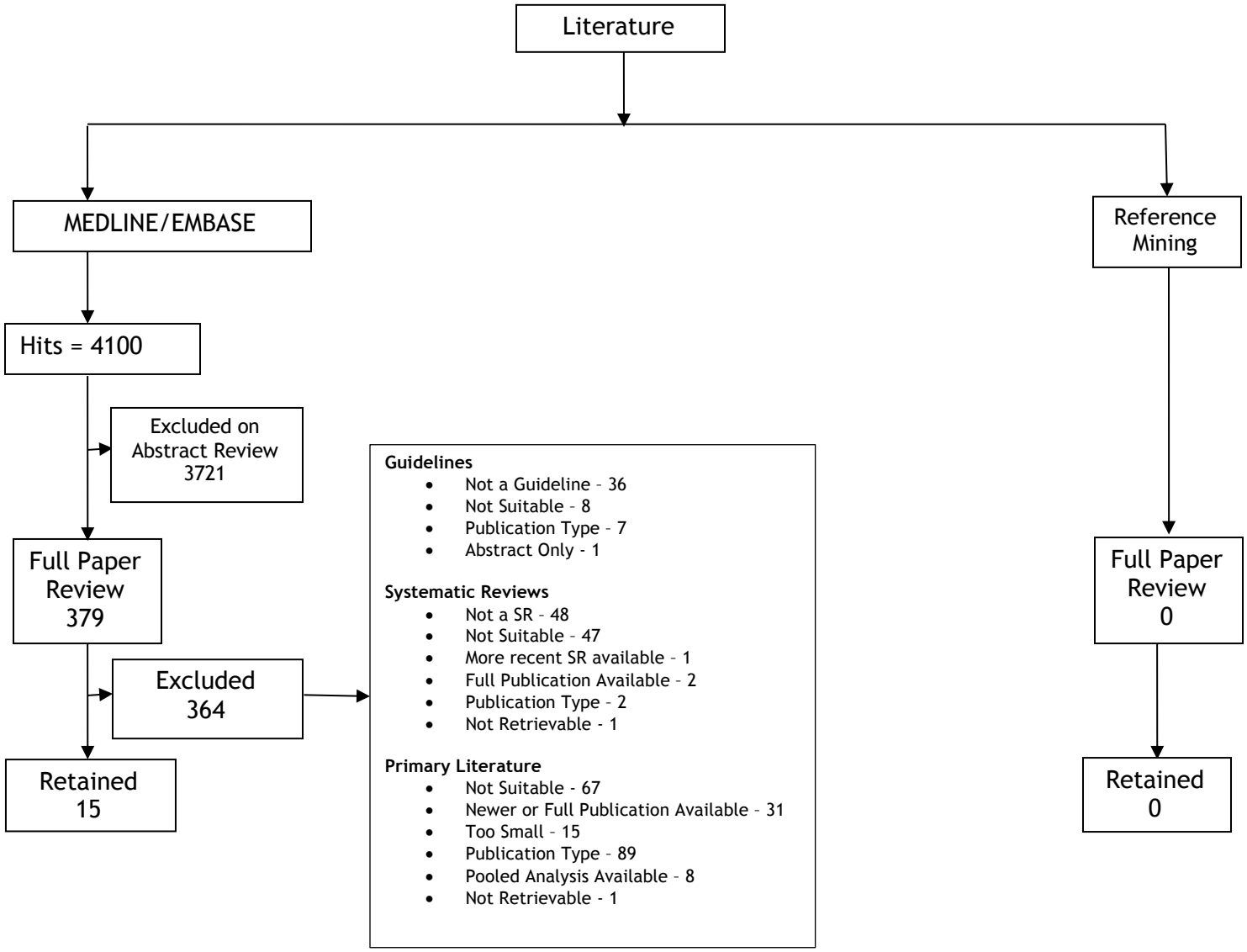

Table 4-1. Studies selected for inclusion.

PATIENT POPULATION	QUESTION	STUDIES RETAINED	REFERENCE MINING	REFERENCES
Resectable CRC Liver Metastases	1. cTACE + systemic treatment vs. systemic treatment alone	0	0	-
	2. DEB-TACE + systemic treatment vs. systemic treatment alone	0	0	-
	3. TARE + systemic treatment vs. systemic treatment alone	0	0	-
Unresectable CRC Liver Metastases – 1st line treatment	4. cTACE + systemic treatment vs. systemic treatment alone	1	0	[1]
	5. DEB-TACE + systemic treatment vs. systemic treatment alone	1	0	[2]
	6. TARE + systemic treatment vs. systemic treatment alone	1*	0	[3,19-23]
Unresectable CRC Liver Metastases – 2nd line treatment	7. cTACE ± systemic treatment vs. systemic treatment alone or BSC alone	0	0	-
	8. DEB-TACE ± systemic treatment vs. systemic treatment alone or BSC alone	3	0	[4-6]
	9. TARE ± systemic treatment vs. systemic treatment alone or BSC alone	4	0	[7-10]

Abbreviations: BSC=best supportive care; CRC=colorectal cancer; cTACE=conventional transarterial chemoembolization; DEB-TACE=drug-eluting bead transarterial chemoembolization; TARE=transarterial radioembolization
*One pooled analysis of 3 randomized trials reported in 6 publications.

Study Design and Quality

Various study designs are included in this guidance document. No systematic reviews were retained. RCTs were assessed using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) (see Table 4-2) and all non-RCTs were assessed using Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/) (see Table 4-3).

Randomized Controlled Trials

Four RCTs published in nine manuscripts [2-4,7,19-23] were included in this guidance document and were assessed using Cochrane's Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) (Table 4-2). One pooled analysis of three RCTs available in six unique publications [3,19-23] was also included. The risk of bias of this study was evaluated as an RCT because the studies were purposively designed a priori to be pooled when they completed. The FOXFIRE/SIRFLOX/FOXFIRE Global pooled analysis was the only RCT that scored 'low' on all domains and could undoubtedly be classified as having a low risk of bias. Three of the included RCTs could not be assessed on at least one element of the risk of bias tool as the information needed was not discussed in the publication. These items were therefore rated as 'unclear'. Overall, two of these three RCTs [2,4] were considered to have an unclear risk of bias. It is conceivable either that this is a reporting issue or that this is both a reporting and methodological issue. One RCT [7] was considered to have a serious risk of bias because one domain was rated as 'high'. This was owing to the significant differences found in several of the baseline characteristics of the participants in each arm of the study (Table 4-2).

Non-Randomized Controlled Studies

This guidance document includes four non-RCTs [1,8-10] that were each assessed using Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/). This tool assesses each trial on seven domains of bias (Table 4-3) as well as an overall assessment of risk of bias. One of the included studies had all domains except one assessed as having a low risk of bias [1]. One of the studies was only available in abstract form and there was not enough information in the abstracts to properly evaluate risk of bias [9]. However, based on the information available the study minimally had a moderate risk of bias. Two of the studies [8,9] did not report on their funding. Overall, two of the included non-randomized studies were assessed as having a moderate risk of bias [1,8], one was assessed as having a high risk of bias [10], and one study could not be properly assessed [9].

Phase II Single-Arm Studies

This guidance document includes two phase II single-arm studies [5,6]. Quality and risk of bias were not assessed in these studies as this type of study design generally has a high risk of bias. Single-arm phase II studies are not intended to be used to guide clinical decision-making. They are intended to be used to guide future research efforts.

Table 4-2. Evaluation of included randomized controlled trials using Cochrane's Risk of Bias tool.

Comparison	Study	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
		Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
Unresectable CRC Liver Metastases - 1st Line Treatment								
DEB-TACE+ST vs. ST	Martin et al. 2015 [2]	Unclear	Unclear	Unclear	Low	Low	Low	High
TARE+ST vs. ST	FOXFIRE/SIRFLOX/FOXFIRE-Global 2017 [3,19-21,23], 2018 [22]	Low	Low	Low	Low	Low	Low	Low
Unresectable CRC Liver Metastases - 2nd LineTreatment								
DEB-TACE±ST vs. ST	Fiorentini et al. 2012 [4]	Low	Unclear	Unclear	Unclear	Low	Low	Low
TARE±ST vs. ST or BSC	Hendlisz et al. 2010 [7]	Low	Unclear	High	Low	Low	Low	Low

Abbreviations: BSC=best supportive care; CRC=colorectal cancer; cTACE=conventional transarterial chemoembolization; DEB-TACE=drug-eluting bead transarterial chemoembolization; ST=systemic treatment; TARE=transarterial radioembolization

Table 4-3. Evaluation of included non-randomized controlled studies using Cochrane's Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I).

Comparison	Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Funding[b]	Overall
Unresectable CRC Liver Metastases - 1st Line Treatment										
cTACE+ST vs. ST	Yu et al. 2016 [1]	Mod	Low	Low	Low	Low	See below[a]	Low	Low	Mod
Unresectable CRC Liver Metastases - 2nd LineTreatment										
TARE±ST vs. ST or BSC	Bester et al. 2012 [8]	Mod	Low	Low	Low	Low	See below[a]	Low	NI	Mod
	Lawal et al. 2012 [9]	Mod	Low	Low	NI	NI	See below[a]	Low	NI	NI
	Seidensticker et al. 2012 [10]	Mod	Low	Low	Low	Low	See below[a]	Low	High	High

Abbreviations: BSC=best supportive care; CRC-colorectal cancer; cTACE=conventional transarterial chemoembolization; DEB-TACE=drug-eluting bead transarterial chemoembolization; Mod=moderate; NI=no information; ST=systemic treatment; TARE=transarterial radioembolization

[a]Low risk for mortality and survival; No information for other outcomes

[b]Low risk = non-industry funding.

Outcomes

Question 1: What is the benefit of the addition of cTACE to systemic therapy in those with resectable CRC liver metastases?

No studies comparing cTACE plus systemic therapy to systemic therapy alone in those with resectable CRC liver metastases were found.

No phase II single-arm studies of cTACE plus systemic therapy in those with resectable CRC liver metastases were found.

Question 2: What is the benefit of the addition of DEB-TACE to systemic therapy in those with resectable CRC liver metastases?

No studies comparing DEB-TACE plus systemic therapy to systemic therapy alone in those with resectable CRC liver metastases were found.

No phase II single-arm studies of DEB-TACE plus systemic therapy in those with resectable CRC liver metastases were found.

Question 3: What is the benefit of the addition of TARE to systemic therapy in those with resectable CRC liver metastases?

No studies comparing TARE plus systemic therapy to systemic therapy alone in those with resectable CRC liver metastases were found.

No phase II single-arm studies of TARE with or without systemic therapy in those with resectable CRC liver metastases were found.

Question 4: What is the benefit of the addition of cTACE to systemic therapy in first-line treatment of those with unresectable CRC liver metastases?

One study [1] was retained. This was a retrospective four-arm study of 154 participants with KRAS wild-type metachronous liver metastases comparing chemotherapy ± cetuximab to chemotherapy ± cetuximab plus cTACE. The chemotherapy regimen used was most often mFOLFOX6 or FOLFIRI. Median survival was significantly different between the study arms (see Table 4-4, $p<0.0001$) as was the five-year PFS ($p<0.0001$) and conversion to resectability (see Table 4-4, $p=0.04$). There were no complete responses. ORR was based solely on partial responses and was significantly different between the study arms ($p=0.001$) (Table 4-4). Multivariate analysis demonstrated that TN stage, tumour response, and treatment group were independent prognostic factors.

Table 4-4. Results of the study evaluating the benefits of the addition of cTACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases.

STUDY ARM	OUTCOME			
	MEDIAN OS (months)	5-YEAR PFS (%)	CONVERSION TO RESECTION (%)	ORR (%)
Chemotherapy	17.5	2.5	7.0	11.6
Chemotherapy + cTACE	28.4	22.3	30.8	46.2
Chemotherapy + Cetuximab	18.9	7.6	10.5	34.2
Chemotherapy + Cetuximab + cTACE	30.3	20.3	32.4	44.1

Abbreviations: CRC=colorectal cancer; cTACE=conventional transarterial chemoembolization; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Question 5: What is the benefit of the addition of DEB-TACE to systemic therapy in first line treatment of those with unresectable CRC liver metastases?

One study [2] was retained. This was a small phase II RCT of 70 participants comparing mFOLFOX (with or without bevacizumab) to mFOLFOX (with or without bevacizumab) plus DEB-TACE using irinotecan (DEBIRI). Unfortunately the participants in the two arms of the trial were not entirely similar at the baseline evaluation. Specifically, the participants in the DEBIRI intervention arm had significantly worse performance status (p=0.042) and more extrahepatic disease (p=0.046) than those in the control arm. The primary end point was response rate. Blinded review using RECIST 1.1 demonstrated no difference in response to treatment between the study arms at two, four, and six months. Blinded review using Choi's criteria demonstrated a significantly better response at two months in the DEBIRI arm compared to the control arm (98% vs. 82%, p=0.01). PFS was similar in the two arms (p=0.18). There were no significant differences between the study arms with respect to downsizing to resection (p=0.05). There were similar rates of grade 3/4 adverse events in the DEBIRI and control arms (Table 4-5). Given that those in the DEBIRI arm were worse off beforehand, the impact of the intervention may be an underestimation of the true effect. However, it is impossible to know how much of an underestimation it was and if the outcomes, which were not significantly different in the two study arms, might then have been significantly different if the study arms had been equivalent.

Table 4-5. Results of the study evaluating the benefits of the addition of DEB-TACE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases.

STUDY ARM	N	RESPONSE RATE (%) (RECIST)	RESPONSE RATE (%) (CHOI)	PFS (mos)	CONVERSION TO RESECTION (%)	OS	TOXICITY (% Grade 3/4)	QOL
mFOLFOX + Bev	30	2 mos – 89 4 mos –95 6 mos - 89	82	15	6	NR	46	NR
mFOLFOX + Bev + DEBIRI	40	2 mos – 88 4 mos –97 6 mos -92 (all ns)	98 p=0.01	12 p=0.18	35 p=0.05 (ns)	NR	54	NR

Abbreviations: Bev=bevacizumab; CRC=colorectal cancer; DEBIRI=DEB-TACE using irinotecan; DEB-TACE=drug-eluting bead transarterial chemoembolization; FOLFOX=folinic acid/fluorouracil/oxaliplatin; mFOLFOX=modified FOLFOX; mos=months; N=number of participants; NR=not reported; ns=not significant; OS=overall survival; PFS=progression-free survival; QOL=quality of life

Question 6: What is the benefit of the addition of TARE to systemic therapy in first line treatment of those with unresectable CRC liver metastases?

One pooled analysis of three RCTs reported in six publications [3,19-23] was retained. The FOXFIRE, SIRFLOX, and FOXFIRE-Global were three individual trials of first-line TARE (using yttrium-90 with resin spheres) plus chemotherapy (± targeted therapy) versus chemotherapy (± targeted therapy) alone that were purposively designed a priori to be combined using individual patient data for analysis of OS. The three trials had very similar eligibility criteria. They were conducted in 14 countries and had a combined enrollment of 1103 participants who were randomly assigned to FOLFOX or FOLFOX plus TARE (single treatment). The FOLFOX chemotherapy regimen was oxaliplatin modified de Gramont in FOXFIRE and mFOLFOX6 in SIRFLOX and FOXFIRE-Global.

Median OS was not significantly different between the FOLFOX and FOLFOX + TARE arms (23.3 months vs. 22.6 months; HR, 1.04; 95% confidence interval [CI], 0.90 to 1.19; p=0.61). Median PFS was also similar in the two treatment arms (10.3 months in the FOLFOX arm vs. 11.0 months in the FOLFOX + TARE arm). There was no significant difference in overall PFS between the study arms (HR, 0.90; 95% CI, 0.79 to 1.02; p=0.11) [3]. However, there was significantly better liver-specific PFS in the FOLFOX + TARE arm (HR, 0.51; 95% CI, 0.43 to 0.62; p<0.001) [19]. ORR was 63% in the FOLFOX arm and 72% in the FOLFOX + TARE arm (odds ratio [OR], 1.52; 95% CI, 1.18 to 1.96; p=0.0012). The rate of downsizing to resection was similar in the two treatment arms (OR, 1.07; 95% CI, 0.78 to 1.48; p=0.67). Grade 3/4/5 adverse events were significantly greater in the FOLFOX + TARE arm (OR, 1.42; 95% CI, 1.09 to 1.85; p=0.0089) [3]. Quality of life measured using the EuroQol EQ-5D-3L was similar in the two treatment arms except at two to three months after baseline. This difference was small and not considered to be clinically significant [3,20]. Quality of life measured using the EORTC QLQ-C30 demonstrated slight impairment in some symptom and function domains in the FOLFOX + TARE arm as well as some improvements at disease progression. None of these differences were considered to be clinically significant [20] (Table 4-6).

Several publications reporting results of subgroup analyses of FOXFIRE-SIRFLOX-FOXFIRE Global have also been recently published. Wasan et al. [21] report that there were no OS differences observed between the treatment arms based on KRAS mutation status. However, OS was significantly greater in the FOLFOX + TARE arm compared to the FOLFOX-alone arm in those with right-sided tumours (22.0 months vs. 17.1 months, p=0.008) but not left-sided tumours (24.6 months vs. 26.6 months, p=0.264) [22]. Similar results with respect to tumour sidedness were obtained when only the SIRFLOX and FOXFIRE Global trials were combined [23].

Table 4-6. Results of the study evaluating the benefits of the addition of TARE to systemic therapy in the first-line treatment of those with unresectable CRC liver metastases.

STUDY ARM	N	OS (months)	MEDIAN PFS (months)	LIVER SPECIFIC PFS	ORR (%)	CONVERSION TO RESECTION (%)	TOXICITY (% Grade 3/4/5)	QOL
mFOLFOX	549	23.3	10.3	HR, 0.51; CI 0.43 to 0.62, p<0.001	63	OR, 1.07; 95%CI, 0.78 to 1.48, p=0.67	OR, 1.42; 95%CI, 1.09 to 1.85, p=0.0089	No clinically significant differences
FOLFOX + TARE	554	22.6 p=0.61	11.0 p=ns		72 p=0.0012			

Abbreviations: CI=confidence interval; CRC=colorectal cancer; FOLFOX=folinic acid/fluorouracil/oxaliplatin; mFOLFOX=modified FOLFOX; N=number of participants; NR=not reported; ns=not significant; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QOL=quality of life; TARE=transarterial radioembolization

Question 7 - What is the benefit of cTACE with or without systemic therapy in second line (or later) treatment of those with unresectable CRC liver metastases?

No studies comparing second-line (or later) cTACE with or without systemic therapy to systemic therapy or BSC alone in those with unresectable CRC liver metastases were found.

No phase II single-arm studies of cTACE with or without systemic therapy in those with unresectable CRC liver metastases were found.

Question 8 - What is the benefit of DEB-TACE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

One small phase III randomized trial of 74 participants comparing DEBIRI to FOLFIRI was retained [4]. OS was significantly longer for those in the DEBIRI arm (22 vs. 15 months, p=0.031, log-rank). PFS was also significantly longer for those in the DEBIRI arm compared to the FOLFIRI arm (7 months vs. 4 months, p=0.006). Similarly, THP was significantly better in the DEBIRI arm (7 months vs. 4 months, p=0.006). ORR was greater in the DEBIRI arm (68.6% vs. 20%) although no p-value was reported. Grade 3 or greater neutropenia (p<0.0001) and mucositis (p=0.00002) occurred more significantly often in those in the FOLFIRI arm. Quality of life was evaluated with the Edmonton Symptom Assessment System. Those in the DEBIRI arm had significantly better physical functioning than those in the FOLFIRI arm at one month (p=0.038), three months (p=0.025) and eight months (p=0.025) after baseline. The median decline in quality of life was significantly shorter in the FOLIRI arm compared to the DEBIRI arm (3 months vs. 8 months, p=0.0002, log-rank). Finally, an evaluation of KRAS demonstrated that within the DEBIRI treatment arm, those with wild-type KRAS had better OS than those with mutated KRAS (26 months vs. 14 months, p=0.017) [4] (Table 4-7).

Two single-arm phase II trials [5,6] were retained. Aliberti et al. [5] studied DEBIRI in 82 participants. Median survival was 25 months and TTP was eight months. Response, defined as shrinkage of target lesions by 50% using RECIST, was 78% three months after DEBIRI. Most adverse events were mild; however, 25% of participants had grade 3 right upper quadrant pain. Di Noia et al. [6] studied DEBIRI plus capecitabine in 40 participants. ORR was 17.5%. Median OS was eight months and median PFS was four months. Grade 3 adverse events occurred in 15% of participants (Table 4-7).

Table 4-7. Outomes of included studies evaluating the benefits of DEB-TACE with or without systemic therapy in the second -line (or later) treatment of those with unresectable CRC liver metastases.

STUDY	STUDY TYPE	STUDY ARM(S)	N	OS (months)	PFS (months)	THP	ORR (%)	TOXICITY (% Grade 3/4)	QOL
Fiorentini et al. 2012 [4]	RCT	FOLFIRI DEBIRI	38 36	Longer in DEBIRI arm, p=0.031, log-rank	4 7 p=0.006	4 7 p=0.006	20 68.6 p=NR	Neutropenia 44 4 p<0.0001 Mucositis 20 1 p=0.00002	Physical Functioning favoured DEBIRI arm at 1 (p=0.038), 3 (p=0.025) and 8 (p=0.025) months. DQOL favoured DEBIRI arm (3 vs. 8 mos), p=0.0002, log-rank
Aliberti et al. 2011 [5]	SA	DEBIRI	82	Median 25	8	NR	NR	25	NR
Di Noia et al. 2019 [6]	SA	DEBIRI + capecitabine	40	Median 8	Median 4	NR	17.5	15	NR

Abbreviations: CRC=colorectal cancer; DEBIRI=DEB-TACE using irinotecan; DEB-TACE=drug-eluting bead transarterial chemoembolization; DQOL=decline in quality of life; FOLFIRI=folinic acid/fluorouracil/irinotecan; mos=months; N=number of participants; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QOL=quality of life; RCT=randomized controlled trial; SA=single arm; THP=time to hepatic progression

Question 9 – What is the benefit of TARE with or without systemic therapy in second-line (or later) treatment of those with unresectable CRC liver metastases?

One small phase III RCT of 46 participants was retained [7]. Usually when randomized data are available, retrospective data are excluded from the analysis of a given guideline question. However, since the retained RCT was so small, it was decided to include the three retrospective studies [8-10] that were found as well. All four studies report median OS. Two studies demonstrate a survival advantage for TARE [8,10] and two studies do not [7,9]. Hendlisz et al. [7] also report median TTP (4.5 vs. 2.1 months, p=0.03) and median TTLP 5.5 vs. 2.1 months, p=0.003), which both demonstrate an advantage for TARE combined with fluorouracil compared to fluorouracil alone. Toxicity was reported in three studies [7,8,10]. Generally adverse events were low grade [8,10] or if there were grades 3 and 4 adverse events they were not significantly different in the study arms [7] (Table 4-8).

Table 4-8. Results of the studies evaluating the benefits of the addition of TARE with or without systemic therapy in second line (or later) treatment of those with unresectable CRC liver metastases.

STUDY	STUDY TYPE	COMPARISON	N	MEDIAN OS (months)	MEDIAN TTP	MEDIAN TTLP (months)
Hendlisz et al. 2010 [7]	RCT	Fluorouracil + TARE Fluorouracil	21 23	10.0 7.3 HR, 0.92; 95%CI, 0.47 to 1.78; p=0.80	4.5 2.1 HR, 0.51; 95%CI, 0.28 to 0.94; p=0.03	5.5 2.1 HR, 0.38; 95%CI, 0.20 to 0.72; p=0.003
Bester et al. 2012 [8] (CRC cohort only)	Retro	TARE BSC/conservative treatment	224 29	11.9 6.6 HR, 0.50*; 95%CI, 0.30 to 0.77*; p<0.001 (log-rank)	NR	NR
Lawal et al. 2012 [9] *abstract*	Retro	TARE Chemotherapy	52 54	8.3 5.8 p=0.316	NR	NR
Seidensticker et al. 2012 [10]	Retro	TARE + BSC BSC	29 29	8.3 3.5 HR, 0.26; 95%CI, 0.15 to 0.48; p<0.001	NR	NR

Abbreviations: BSC=best supportive care; CI=confidence interval; CRC=colorectal cancer; HR=hazard ratio; OS=overall survival; RCT=randomized controlled trial; Retro=retrospective; TARE=transarterial radioembolization; TTLP=time to liver progression; TTP=time to progression
*Read off of a graphical representation in Figure 2 in the publication at 300% enlargement

Ongoing, Unpublished, or Incomplete Studies

A randomized phase III trial comparing Hepatic Arterial Injection of Yttrium-90 resin microspheres (SIR-spheres) plus systemic maintenance therapy versus systemic maintenance therapy alone for patients with unresectable liver metastases from colorectal cancer which are controlled after induction systemic therapy	
Protocol ID:	NCT01895257
Date last modified:	July 7, 2017
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Time to first progression
Accrual:	162 will be accrued
Sponsorship:	Universiteit Antwerpen
Status:	Recruiting

A phase III clinical trial evaluating TheraSphere® in patients with metastatic colorectal carcinoma of the liver who have failed first line chemotherapy	
Protocol ID:	NCT01483027
Date last modified:	February 1, 2019
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Progression free survival, Hepatic Progression free survival
Accrual:	428 accrued
Sponsorship:	BTB International Inc., Biocompatibles UK Ltd.
Status:	Active, not ecruiting

A randomized phase I/III study of systematic chemotherapy with or without hepatic chemoembolization for liver-dominant metastatic adenocarcinoma of the colon and rectum	
Protocol ID:	NCT00023868
Date last modified:	January 6, 2009
Type of trial:	Randomized study, parallel assignment, active control
Primary endpoint:	Not provided
Accrual:	315 will be accrued
Sponsorship:	American College of Radiology Imaging Network, National Cancer Institute
Status:	Recruitment Completed

Drug-eluting bead, Irinotecan (DEBIRI) therapy of liver metastasis from colon cancer with concomitant systemic oxaliplatin, fluorouracil and leucovorin chemotherapy, and anti-angiogenic therapy	
Protocol ID:	NCT00932438
Date last modified:	April 18, 2013
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Tumour response
Accrual:	70 accrued
Sponsorship:	University of Louisville, Biocompatibles UK Ltd.
Status:	Completed

Protocol ID:	
Date last modified:	
Type of trial:	
Primary endpoint:	
Accrual:	
Sponsorship:	
Status:	

DISCUSSION

The treatment of CRC liver metastases challenges conventional oncology dogma: that local therapy should be reserved for local disease, while systemic therapy should be offered to patients with systemic disease. Liver metastases unequivocally represent systemic disease, yet strong evidence supports the application of local therapies (surgical resection, ablation) for patients with resectable, liver-predominant metastases. Indeed, a substantial proportion of patients will be cured with resection of all visible liver metastases.

In patients with unresectable liver-predominant metastases, conventional treatment is systemic therapy. The benefit of local therapies in patients with limited disease naturally raises the possibility that liver-directed regional therapies may provide benefit in patients with more extensive liver-predominant metastases. Regional approaches to delivery of chemotherapy or radiation have been developed and investigated for over 50 years. The relative paucity of evidence exploring these techniques compared with conventional systemic therapy highlights some of the challenges in delivery and evaluation of regional therapies.

Hepatic arterial anatomy is highly variable, requiring sophisticated equipment and expertise to deliver therapy. Options include intermittent percutaneous access by interventional radiologists with delivery of therapeutic agents bound to beads that slowly diffuse into the hepatic parenchyma between treatments, or implantation of arterial ports or pumps to allow more frequent treatment with boluses or infusion of drugs. In contrast, delivery of systemic therapy is simpler and standardized through a venous access device. Thus, delivery of regional therapies requires multidisciplinary care at dedicated centres.

Selection of patients who are likely to benefit from regional therapies is also challenging. A small subset of patients has liver-only metastases and are ideal candidates for this therapy. The majority of patients with extensive liver metastases will also have some disease outside the liver. Patterns of progression in patients with liver-predominant metastases are variable and difficult to predict, but without knowing this it is challenging to identify patients who could benefit from regional therapies to the liver.

The data summarized in this guideline are limited by these practical considerations. HAI pump chemotherapy has the most robust supporting data of all regional approaches but is not included in this guideline. Please refer to the dedicated companion guideline [2-30b: Hepatic Arterial Infusion for Colorectal Liver Metastases] for a full discussion of this therapy. Our search for evidence related to other regional therapies identified very little strong evidence in either direction.

cTACE is a technique commonly used to treat patients with hepatocellular carcinoma (HCC), with good effect. However, HCC is a hypervascular tumour and most of the effect likely comes from ischemia through embolization of target vessels rather than drug delivery. In contrast, CRC metastases are most commonly hypovascular, and embolization is unlikely to be effective. Our search only identified one non-randomized study examining cTACE in patients with CRC liver metastases. This technique has largely been replaced by DEB-TACE, which allows better delivery of drugs to the liver parenchyma.

We identified four small trials of DEB-TACE [2,4-6], two of which were randomized [2,4]. These studies suggest a benefit in terms of OS, PFS, and quality of life in the second-line setting, although the strength of evidence is low owing to the small sample size. Treatment with DEB-TACE may provide benefit to patients with liver-predominant metastases who have progressed on first-line systemic therapy. Ideally, other larger trials would be done in this setting; however, given the complexities in delivery of this therapy this may not be practical. In the absence of more robust evidence, clinicians should discuss this treatment option with patients who may benefit and balance patient preferences and values with the uncertainty of the evidence.

In contrast, three randomized trials have been conducted including over 1100 patients examining the effectiveness of TARE in patients with liver-predominant metastases. While there were subtle differences among trials, the overall design was similar and the results were pooled in a pre-planned analysis [3]. The findings were disappointing and speak to the challenges alluded to in identifying patients who are likely to benefit from regional therapies. TARE had a clear effect on the liver metastases: the HR for liver-specific PFS was 0.51 with a narrow 95% CI (0.43 to 0.62). However, despite the improvement in liver metastases, the patient-important outcomes of PFS, OS, and quality of life did not differ between groups. While TARE appears to control the disease within the liver, it should not be offered to patients in the absence of a benefit in patient-important outcomes. Further research may focus on patient populations who have the potential to benefit from better control of liver metastases, such as liver-only disease in the second-line setting.

Our search did not identify any strong evidence for the use of regional therapies (cTACE, DEB-TACE, and TARE) to reduce recurrence in patients with resectable CRC liver metastases. These therapies are not recommended in this setting outside of a clinical trial, although further research is needed.

CONCLUSIONS

Limited evidence supports the use of percutaneous regional therapies in patients with unresectable CRC liver metastases. There are strong data demonstrating positive effects of TARE within the liver, but they do not translate to a benefit in patient-important outcomes. DEB-TACE appears to offer a survival benefit in the second-line setting, although the evidence is limited by small sample size and larger trials are needed.

Regional Therapies for Colorectal Cancer Liver Metastases

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1 and 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 24 members of the GDG Expert Panel, 18 members cast votes and no one abstained, for a total of 75% response in July 2019. Of those that cast votes, 18 approved the document 100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. A comment to update the statistics in the introduction.	This was done.
2. Consider adding a glossary of terms.	This was done.
3. Clarify the Interpretation of Evidence section for the recommendations.	This was done.
4. Indicate that there is a companion guideline covering HAI for CRC liver metastases under development.	This was done.
5. A question why radiofrequency thermal ablation, etc., wasn't addressed in the guideline?	This was beyond the scope of the guideline, which was only meant to address regional therapies.
6. A comment about the wording of Recommendation 5.	This was adjusted to make it clearer.
7. Comments about why some recommendations include a statement about multidisciplinary case conferences and others do not.	Clarifications were added to certain sections of the text to address this concern.
8. Several minor editorial-type changes.	These were all corrected.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in May 2019. The RAP approved the document on May 13, 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from the RAP.

Comments	Responses
1. Add some information on Working Group deliberations when making recommendations.	This was done.
2. Clarify statements regarding threshold criteria.	This was done.
3. Add information regarding the implications of the statistical differences in the arms at the outset of the Martin et al. study for Question 5.	This was done.

Patient- and Caregiver-Specific Consultation Group

Three cancer patient survivors participated as Consultation Group members. They reviewed this document in May 2019. The main comments from this Consultation Group and the Working Group's responses are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group.

Comments	Responses
1. There were no comments that required modifications. They felt the recommendations were clear and unambiguous even though there were no recommendations for doing a particular intervention; only one recommendation to not do a particular intervention.	No changes needed.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Eight targeted peer reviewers from Ontario, British Columbia, Alberta and the USA who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Four agreed to be the reviewers (Appendix 2). Four responses were received. Results of the feedback survey are summarized in Table 5-4. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	2
2. Rate the guideline presentation.			1		3
3. Rate the guideline recommendations.			1	1	2
4. Rate the completeness of reporting.		1			3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			2		2
6. Rate the overall quality of the guideline report.			1	1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.		1	1		2
8. I would recommend this guideline for use in practice.		1	1		2
9. What are the barriers or enablers to the implementation of this guideline report?	• There is little phase III evidence outside of the TARE data in the unresectable population • Current funding, and skillset of multidisciplinary expertise in colorectal liver metastases				

Table 5-5. Responses to comments from targeted peer reviewers.

Comments	Responses
1. A suggestion that we include single-arm studies for the review of TARE	We have not made this change. If good RCT data are available, we do not use other types of studies.
2. A suggestion that we clarify how the patient reviewers were identified.	We have made this clarification.
3. A suggestions to provide definitions for 'unresectable disease' and 'liver-dominant disease' even though these terms are very hard to define.	We have added in definitions for these terms.
4. A suggestion to include NCCN recommendations for the use of TARE.	We have not made this change. NCCN guidelines are not based on a systematic review and therefore are not eligible for inclusion in PEBC guidelines.
5. A suggestion to add HAI to the scope of the guideline.	HAI is the topic of a separate, companion guideline. This is noted in the current document.
6. A statement that local therapies should be considered prior to regional therapies.	We have clarified this point in the document.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, radiation oncologists, surgical oncologists and interventional radiologists in the PEBC database were contacted by email to inform them of the survey. Additionally, volunteer interventional radiologists were sought from OH (CCO)'s Interventional Radiology Steering Committee. A total of 380 clinicians, all from Ontario, were contacted. Thirty-one responses were received. Sixteen stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 15 people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Number 15 (4.3%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1(7)		2(13)	3(20)	9(60)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			2(13)	4(27)	9(60)
3. I would recommend this guideline for use in practice.		1(7)	1(7)	3(20)	10(67)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Too few trials and poor-quality trials. • Lack of definitive evidence for benefit or harm. Enablers: • Robust data review • Great job framing recommendations despite lack of quantity and quality of data. • Guideline is based on RCT evidence • Guideline will be useful in case conference discussions				

Table 5-7. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	**Responses**
1. A suggestion that Recommendations 6 and 7 should be more strongly worded against using these interventions.	The Working Group felt that the wording was sufficient and that allowing for use of these interventions on a case-by-case basis was reasonable.
2. A suggestions that the use of the terms DEB-TACE and DEBIRI are confusing.	This was clarified in the document.
3. A suggestion that it should be clarified if a given study of TARE used resin or glass based spheres.	This clarification was made.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1. Members of the Regional Therapies for Colorectal Cancer Liver Metastases Guideline Development Group

Name	Specialty	Affiliation
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Mala Bahl	MO	Grand River Regional Cancer Centre Kitchener, ON
Robert Beecroft	IR	Mount Sinai Hospital Toronto, ON
Scott Berry	MO	Odette Cancer Centre Toronto, ON
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre Ottawa, ON
Mark Doherty	MO	Odette Cancer Centre Toronto, ON
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON
Elena Elimova	MO	Princess Margaret Hospital Toronto, ON
Valerie Francescutti	SO	Hamilton Health Sciences Hamilton, ON
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON
Julie Hallet	SO	Odette Cancer Centre Toronto, ON
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON
Raymond Jang	MO	Princess Margaret Hospital Toronto, ON
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON

Richard Malthaner	SO	London Regional Cancer Program London, ON
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON
Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, ON
Stephen Welch	MO	London Regional Cancer Progam London, ON
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, ON

Abbreviations: HRM=health research methodologist; IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Appendix 2. Members of the Regional Therapies for Colorectal Cancer Liver Metastases Working Group, Expert Panel, Report Approval Panel and Target Reviewers and their COI declarations.

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group), Non-Surgical Management of Hepatocellular Carcinoma Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Members of the Non-Surgical Management of Hepatocellular Carcinoma Working Group

Name	Specialty	Affiliation	Declarations of interest
Paul Karanicolas Working Group Co-Chair	SO	Odette Cancer Centre Toronto, ON	Within the past 5 years has received $5000 or more in a single year to act in a consulting capacity for Sanofi. Is the surgery lead for HAIP program at Sunnybrook but this intervention is not within the scope of this guideline.
Rob Beecroft Working Group Co-Chair	IR	Mount Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Elizabeth David	IR	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, ON	Within the past 5 years has received $5000 or more in a single year to act in a consulting capacity for Integra and Novartis. Within the past 5 years has received $5000 or more in a single year for a laparoscopic liver surgery course with Integra. Within the past 5 years has received grant support from Bayer and Roche.
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest.
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest.
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, Ontario	Declared they had no conflicts of interest.

Abbreviations: HRM=health research methodologist; IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Regional Therapies for Colorectal Cancer Liver Metastases Guideline Development Group Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Received $500 or more in a single year to act in a consulting capacity for Amgen, Shire, Celgene, Roche, Pfizer, Apobiologix, and Sanofi. Received grants from Amgen, Roche, Merck, Pfizer, Bristol-Meyers Squibb, Boston Biomedical Inc. and Array. Had managerial responsibility and received $5000 or more in a single year from Roche Fellowship Program.
Mala Bahl	MO	Grand River Regional Cancer Centre Kitchener, ON	Declared they had no conflicts of interest.
Scott Berry	MO	Odette Cancer Centre Toronto, ON	Received $500 or more in a single year to act in a consulting capacity for Taiho and Amgen. Received $5000 or more in a single year as Medical Director for OncologyEducation.com.
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON	Declared they had no conflicts of interest.
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Mark Doherty	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON	Received $500 or more in a single year to act in a consulting capacity for Merck, Novartis and Amgen.
Valerie Francecutti	SO	Hamilton Health Sciences Hamilton, ON	Declared they had no conflicts of interest.
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Received $500 or more in a single year to act in a consulting capacity for Amgen, Taiho, Novartis and Ipsen. Received grants from Ipsen and Novartis.
Julie Hallet	SO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest.
Raymond Jang	MO	Princess Margaret Hospital Toronto, ON	Received $500 or more in a single year to act in a consulting capacity for Novartis and

			Ipsen. Received grants from AstraZeneca, Merck, Novartis, Eli Lily, Boston Biomedical, Bristol-Myers Squibb.
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Richard Malthaner	SO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest.
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON	Received $500 or more in a single year to act in a consulting capacity for Amgen, Taiho.
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON	Declared they had no conflicts of interest.
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest.
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON	Declared they had no conflicts of interest.
Stephen Welch	MO	London Regional Cancer Progam London, ON	Was the local PI for the EPOCH study (BTG-Theraspheres).
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest.

Abbreviations: IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Regional Therapies for Colorectal Cancer Liver Metastases Guideline Development Group Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Melissa Brouwers	HR	School of Epidemiology and Public Health, University of Ottawa Ottawa, ON	Declared they had no conflicts of interest
Jonathan Sussman	RO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Laurie Elit	SO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest

Abbreviations: HR=health research methodologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Regional Therapies for Colorectal Cancer Liver Metastases Guideline Development Group Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Sean Cleary	SO	Mayo Clinic	Within the past 5 years received $500 or more in a single year to act as an education consultant for Ethicon Olympus. Within the past 5 years has been a principal investigator for the EMERALD-2 Trial funded by AstraZeneca.
Laura Dawson	RO	Princess Margaret Hospital	Within the past 5 years has been a co-investigator on a grant from Merck on immunotherapy and radiation for HCC (not related). Within the past 5 years has been a principal investigator of a study of patients with advanced HCC (not related).
Howard Lim	MO	BC Cancer Agency	In the past 5 years has received $500 or more in a single year to act in a consulting capacity for Roche, Eisai, Taiho, Amgen, Ipsen, BMS, Lilly and Therasphere. In the past 5 years has received $500 or more in a single year for other financial or material support from Eisai and Taiho. Within the past 5 years has been a principal investigator for the following trials: first line gastric cancer with Ramicirumab, first line gastric cancer with anti-caludin AB (AstraZeneca); CO 26 in metastastic CRC (AstraZeneca). Aided in the funding model for DEB-TACE and Y-90 for HCC in British Columbia.
David Liu	IR	University of British Columbia	Within the past 5 years received $500 or more in a single year to act in a consulting capacity for Ethicon Endosurgery

Abbreviations: IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

The conflicts of interest declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

Appendix 3: Literature Search Strategies for Clinical Practice Guideline, Systematic Review and Primary Literature

Clinical Practice Guidelines

MEDLINE

1. exp Colorectal Neoplasms/
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp Evidence-Based Practice/
7. guideline.pt.
8. exp Guideline/ or exp Practice Guideline/
9. practice parameter$.tw.
10. practice guideline$.mp.
11. (guideline: or recommend: or consensus or standards).ti.
12. (guideline: or recommend: or consensus or standards).kw.
13. or/6-12
14. 5 and 13
15. limit 14 to yr="2014 -Current"
16. limit 15 to english language

EMBASE

1. colorectal neoplasms.mp. or exp colorectal tumor/
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp evidence based practice/
7. exp practice guideline/
8. guideline.pt.
9. practice parameter$.tw.
10. practice guideline$.mp.
11. (guideline: or recommend: or consensus or standards).ti.
12. (guideline: or recommend: or consensus or standards).kw.
13. or/6-12
14. 5 and 13
15. limit 14 to english language
16. limit 15 to yr="2014 -Current"

Systematic Reviews

MEDLINE

1. exp Colorectal Neoplasms/
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp Meta-Analysis as Topic/
7. meta-analysis.pt.
8. (systematic adj (review: or overview:)).mp.
9. (meta-analy: or metaanaly: or meta analy:).mp.
10. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
11. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
12. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
13. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
14. or/6-13
15. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
16. (stud: adj1 select:).ab.
17. (15 or 16) and review.pt.
18. 14 or 17
19. 5 and 18
20. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
21. 19 not 20
22. limit 21 to yr="2005 -Current"

EMBASE

1. colorectal neoplasms.mp. or exp colorectal tumor/
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp meta analysis/
7. exp "meta analysis (topic)"/
8. exp "systematic review"/
9. exp "systematic review (topic)"/
10. (meta analy$ or metaanaly$ or meta-analy$).tw.
11. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
12. (systematic adj (review$ or overview$)).tw.
13. exp "review"/ or review.pt.
14. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
15. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
16. or/6-15
17. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
18. (study adj selection).ab.
19. (17 or 18) and review.pt.
20. 16 or 19
21. 5 and 20
22. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
23. 21 not 22
24. limit 23 to yr="2005 -Current"
25. limit 24 to english language

Primary Studies

MEDLINE

1. exp Colorectal Neoplasms/
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp CHEMOEMBOLIZATION, THERAPEUTIC/
7. transarterial chemoembolization.mp.
8. transcatheter arterial chemoembolization.mp.
9. exp Catheter Ablation/
10. TACE.mp.
11. DEB-TACE.mp.
12. drug eluting bead$.mp.
13. DEBIRI.mp.
14. or/6-13
15. transarterial radioembolization.mp.
16. exp YTTRIUM RADIOISOTOPES/ or exp YTTRIUM/ or exp YTTRIUM ISOTOPES/
17. selective internal radiation therapy.mp.
18. selective internal radiation treatment.mp.
19. SIRT.mp.
20. TARE.mp.
21. or/15-20
22. 14 or 21
23. 5 and 22
24. limit 23 to yr="1990 -Current"
25. limit 24 to english language
26. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
27. 25 not 26
28. animal/ not (exp human/ or humans/)
29. 27 not 28

EMBASE

1. exp colorectal tumor/ or colorectal neoplasms.mp.
2. ((colorectal or colon or colonic or rectal or rectum or rectosigmoid) adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. ((liver or hepat$) adj2 (metasta$ or spread$)).mp.
5. 3 and 4
6. exp chemoembolization/
7. transcatheter arterial chemoembolization.mp.

8. exp catheter ablation/
9. TACE.mp.
10. DEB-TACE.mp.
11. drug eluting bead$.mp.
12. DEBIRI.mp.
13. or/6-12
14. transarterial radioembolization.mp. or exp radioembolization/
15. exp microsphere/
16. exp yttrium/ or exp yttrium 90/ or exp yttrium 86/
17. selective internal radiation therapy.mp.
18. selective internal radiation treatment.mp.
19. SIRT.mp.
20. TARE.mp.
21. or/14-20
22. 13 or 21
23. 5 and 22
24. limit 23 to yr="1990 -Current"
25. limit 24 to english language
26. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
27. 25 not 26
28. animal/ not (exp human/ or humans/)
29. 27 not 28