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Guideline 2-30b

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

Hepatic Arterial Infusion for Colorectal Liver Metastases

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An assessment conducted in December 2025 deferred the review of Guideline 2-30b. 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 2-30b is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/69331

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PUBLICATIONS RELATED TO THIS REPORT
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Hepatic Arterial Infusion for Colorectal Liver Metastases

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 the use of hepatic arterial infusion (HAI) in the treatment of patients with colorectal cancer (CRC) liver metastases with respect to overall survival, disease-free survival, progression-free survival (PFS), and hepatic PFS.

TARGET POPULATION

These recommendations apply to adults with liver metastases from CRC.

INTENDED USERS

The intended users of this guideline are healthcare providers involved in the delivery of care of adults with liver metastases from CRC.

RECOMMENDATIONS

Recommendation 1
There is insufficient evidence to recommend the addition of HAI to systemic therapy (ST) in patients with resectable or resected CRC liver metastases.

Recommendation 2
There is insufficient evidence to recommend the addition of HAI to ST in the first-line setting in patients with unresectable CRC liver metastases.

Recommendation 3
The addition of HAI to ST in the second-line or later setting in patients with unresectable CRC liver metastases is not recommended.

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Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations regarding the use of hepatic arterial infusion (HAI) in the treatment of patients with colorectal cancer (CRC) liver metastases with respect to overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and hepatic PFS.

TARGET POPULATION

These recommendations apply to adults with liver metastases from CRC.

INTENDED USERS

The intended users of this guideline are healthcare providers involved in the delivery of care of adults with liver metastases from CRC.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1
There is insufficient evidence to recommend the addition of HAI to systemic therapy (ST) in patients with resectable or resected CRC liver metastases.
Key Evidence for Recommendation 1
• Two randomized trials were retained. The Kemeny et al. [1,2] trial, published in 1999, had dual primary endpoints of OS and PFS at two years. Results showed a significant increase in two-year OS for adjuvant HAI plus ST as compared with ST alone (86% vs. 72%, p=0.03), while the two-year PFS between the two groups was not significant (57% vs 42%, p=0.07). Moreover, this trial was published prior to the advent of modern chemotherapeutic regimens and local therapies, limiting its applicability in the modern context. • The Kusano et al. trial [3], published only in abstract form in 2018, accrued 44 of a planned 280 patients, and was terminated early due to slow accrual. The reported three-year DFS and OS were worse in the experimental arm but not statistically significant (43.5% vs. 58%; hazard ratio [HR], 1.304; p=0.534, and 80.2% vs. 85.2%; HR, 2.255; p=0.192, respectively). There was no significant difference in the frequency of grade 3 or higher toxicities between the two arms. • Both trials, when assessed by the Cochrane Risk of Bias tool, had high risk of bias owing to lack of blinding. • Seven non-randomized comparative studies were included [4-10], four of which demonstrated significant survival improvements with the addition of HAI [4,5,7,8]. Two studies [9,10] were subsets from the same database used in Groot Koerkamp et al. [7] and also demonstrated significant survival benefits with the addition of HAI. However, all these studies had a high risk of bias.
Justification for Recommendation 1
There is only one fully published randomized phase III trial [1,2] in this setting which, while showing a significant improvement in one of its two primary survival endpoints, was published in an era prior to availability of several contemporary systemic chemotherapy options. In

addition, local management of colorectal liver metastases has evolved substantially in liver-directed therapies including specialized radiation and surgery techniques. Therefore, based on a single dated trial, there was agreement among the Working Group members that benefit of the addition of HAI to ST in patients with resectable or resected colorectal liver metastases remains unknown. The management of the toxicities associated with HAI were considered by the Working Group to be generally manageable, but only by clinicians with specialized training in HAI.

The more recent randomized trial by Kusano et al. [3] was closed early with only 16% of the planned accrual and is therefore underpowered to detect its primary endpoint of three-year DFS. The study had consistent trends of decreased survival parameters, and thus did not demonstrate any benefit to the addition of HAI to ST.

Overall, the Guideline Development Group concluded that HAI should only be available to patients if offered in a modern clinical trial.

Recommendation 2

There is insufficient evidence to recommend the addition of HAI to ST in the first-line setting in patients with unresectable CRC liver metastases.

Key Evidence for Recommendation 2

- No randomized controlled trial (RCT) evidence was available for this question.
- One small comparative study of 51 patients [11] demonstrated a significant improvement in median OS (18.5 months vs. 13.0 months, p=0.0312). Methods and statistical design were not provided, and the trial had a high risk of bias.
- Three additional single-arm studies were retained [12-14]. As these are small and non-comparative, they cannot contribute to the formation of recommendation regarding the addition of HAI to ST in this population.

Justification for Recommendation 2

The certainty of the evidence is low. The magnitude of benefit for the desirable outcomes of survival is uncertain based on the available evidence. The management of the toxicities associated with HAI are generally manageable by clinicians with specialized training in HAI. The available data are insufficient to warrant a recommendation for the addition of HAI to ST in this population outside of a modern clinical trial.

Recommendation 3

The addition of HAI to ST in the second-line or later setting in patients with unresectable CRC liver metastases is not recommended.

Key Evidence for Recommendation 3

- No RCT evidence was available for this question.
- Two small retrospective comparative studies [15,16] were available. The first demonstrated a significant improvement in median OS, as well as hepatic

progression free survival and PFS [15]. The second demonstrated an improvement in median OS [16]. Both trials were assessed as having a high risk of bias.
- Eight single-arm studies in nine publications were retained [17-25]. As these are small and non-comparative, they did not contribute to the formation of a recommendation regarding the addition of HAI to ST in this population.

Justification for Recommendation 3

The certainty of the evidence is low. The magnitude of benefit for the desirable outcomes of survival is uncertain based on the available evidence. The management of the toxicities associated with HAI are generally manageable by clinicians with specialized training in HAI. The available data are insufficient to warrant a recommendation for the addition of HAI to ST in this population outside of a modern clinical trial.

IMPLEMENTATION CONSIDERATIONS

None.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-30a: Regional Therapies for Colorectal Cancer Liver Metastases (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/63286)
- PEBC Evidence-based Series #17-7: *Liver Resection for Colorectal Metastases* (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2236)

FURTHER RESEARCH

Good-quality RCT data regarding the addition of HAI to ST, for specific patient populations in either the adjuvant or metastatic setting, would allow for recommendations based on sufficient evidence rather than recommendations based on poor or insufficient evidence.

GUIDELINE LIMITATIONS

The Working Group for this guideline did not include patient representatives. Thus, when developing recommendations, input from patients about their values and preferences was not sought and a systematic review for this information was not performed. Working Group members used their prior clinical experiences with those with CRC to assume the relevant values and preferences.

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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 Program in Evidence-Based Care (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.

JUSTIFICATON FOR GUIDELINE

This topic was prioritized by the Gastrointestinal Disease Site Group because there is a lack of suitable guidance as well as inconsistencies in practice. Initially, an evidence summary was created but it was decided that a full guideline was warranted. This guideline will be part of a series of guidelines regarding the treatment of CRC liver metastases (see 2-30a).

GUIDELINE DEVELOPERS

This guideline was developed by the Hepatic Arterial Infusion for Colorectal Liver Metastases GDG (Appendix 1).

The project was led by a small Working Group of the Hepatic Arterial Infusion for Colorectal Liver Metastases GDG, 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 medical oncology, radiation oncology, surgical oncology, and health research methodology. Other members of the Hepatic Arterial Infusion for Colorectal Liver Metastases GDG 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 GDG members 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 [26,27]. 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 [28] 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 and to improve the completeness and transparency of reporting in practice guidelines.

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 evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) 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 Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed at least one research question (see Section 4) were included. Guidelines older than three years were excluded. Guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines on March 17, 2021: National Institute for Health and Care Excellence Evidence Search (NICE), Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, Cancer Council Australia, Standards and Guideline Evidence (SAGE) and National Guidelines Clearinghouse. MEDLINE and EMBASE databases were also searched.

The guideline search included guidelines published in 2015 and later. Practice guideline databases and guideline developer websites did not yield any relevant current guidelines that met the inclusion criteria. The MEDLINE and EMBASE searches yielded 27 hits in total of which none underwent full-text review. No existing current guideline was 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.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

ACKNOWLEDGEMENTS

The Hepatic Arterial Infusion for Colorectal Liver Metastases GDG would like to thank the following individuals for their assistance in developing this report:

- Laurie Elit, Bill Evans, Ryan Fields, Sharlene Gill, Sheila McNair, Jonathan Sussman, Xiaomei Yao, 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 second most common cancer, accounting for 11.9% of all cancers in Canada. It is the second leading cause of cancer deaths in men and the third leading cause of cancer deaths in women. Approximately 26,900 Canadians (14,900 men and 12,000 women) will be diagnosed with CRC in 2020 [29].

Importantly, the liver is the most common site of involvement, with synchronous metastases present in approximately 25% of patients at diagnosis and nearly 50% of patients developing liver metastases during the course of the disease [30]. Hepatic resection, often combined with ST (either perioperatively or postoperatively), remains the only curative treatment option; the five-year and 10-year cancer-specific survival rates are 36% and 23%, respectively [31]. Despite advances in surgical and other local techniques, only 15% of patients have colorectal liver metastases that are deemed resectable at the time of presentation. For patients with unresectable disease, survival rates are generally poor and do not exceed 2% at five years [32,33]. Recent improvements in systemic therapy regimens have increased survival for these patients and have enabled a subset to be sufficiently down staged to allow for potentially curative resections. Nonetheless, relapse occurs in up to 60% of patients following hepatectomy with one-half of these recurrences confined to the liver [34-36].

Given that normal liver parenchyma receives most of its blood supply from the portal vein, whereas liver metastases are perfused almost exclusively by the hepatic artery, a great deal of interest had been placed on liver-directed therapies [37]. One such strategy is HAI, which enables the direct delivery of higher drug concentrations to the tumour while potentially minimizing systemic toxicity. HAI can be administered via a percutaneously placed catheter, an arterial access port, or a surgically implantable subcutaneous pump [38]. To date, HAI has not been widely adopted as there is a lack of guidance on its precise role in the overall management of CRC liver metastases. Additionally, the chemotherapeutic commonly used in HAI is not a commercially approved drug in Canada. The purpose of this report is to synthesize the evidence surrounding the role of HAI in the treatment of patients with CRC liver metastases.

This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42019131677 (https://www.crd.york.ac.uk/PROSPERO/#recordDetails).

RESEARCH QUESTIONS

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

1) What is the benefit of the addition of HAI to ST in patients with resectable or resected CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

2) What is the benefit of the addition of HAI to ST in first-line treatment in patients with unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

3) What is the benefit of the addition of HAI with or without ST in second-line (or later) treatment of unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

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 Systematic Reviews

A search was conducted for existing systematic reviews.

- Databases searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews
- Years covered: 2000 to present
- Search terms: See Appendix 3
- Selection criteria:
    - English language systematic review that covered any of the current guideline questions with similar inclusion/exclusion criteria; and
    - The review comprehensively searched at least one database with the literature search date and search terms included; and
    - The review included an assessment of the quality of the evidence; and
    - The review extracted relevant information from each study; and
    - The review analyzed the data appropriately.

If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per research comparison was selected by RC based on its age, quality, and the best match with our study selection criteria stated below.

Search for Primary Literature

For each outcome per comparison, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

The primary literature was searched using MEDLINE (1990 to March 17, 2021) and EMBASE (1990 to March 17, 2021) databases through OVID. In addition, annual meetings from the American Society of Clinical Oncology (ASCO), the Gastrointestinal Cancers Symposium (ASCO GI), the Society of Surgical Oncology, the Americas Hepato-Pancreato-Biliary Association (AHPBA) and the European Society for Medical Oncology (ESMO) were searched up to March 2021 for relevant abstracts. Likewise, reference lists from relevant systematic reviews and primary literature were scanned for potentially useful studies (see Appendix 3 for the full search strategy).

Study Selection Criteria and Process

Question 1 - What is the benefit of the addition of HAI to ST in patients with resectable or resected CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

Inclusion Criteria

- English language
- Adults with resectable or resected CRC liver metastases
- Includes a comparison of interest: HAI + ST versus ST alone
- Includes at least one outcome of interest (OS, DFS, time to progression [TTP], PFS, toxicity/safety, quality of life [QOL])
- 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: 1990 to present

Exclusion Criteria

- Case studies, commentaries, editorials

Question 2 - What is the benefit of the addition of HAI to ST in first-line treatment in patients with unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

Inclusion Criteria

- English language
- Adults with unresectable CRC liver metastases, first-line treatment
- Includes a comparison of interest: HAI + ST versus ST alone
- Includes at least one outcome of interest (OS, DFS, TTP, PFS, hepatic PFS, toxicity/safety, QOL)
- 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: 1990 to present

Exclusion Criteria

- Case studies, commentaries, editorials

Question 3 - What is the benefit of HAI with or without ST in second-line (or later) treatment of patients with unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

Inclusion Criteria

- English language
- Adults with unresectable CRC liver metastases, second-line (or later) treatment
- Includes a comparison of interest: HAI ± ST versus ST alone or best supportive care alone
- Includes at least one outcome of interest (OS, DFS, TTP, PFS, hepatic PFS, toxicity/safety, QOL)
- 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: 1990 to present

Exclusion Criteria

- Case studies, commentaries, editorials

A review of the titles and abstracts was conducted by one reviewer (RC) independently. For studies that warranted full-text review one reviewer (RC) reviewed each study independently. If uncertainty existed, the Working Group lead (JB) was consulted.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by RC independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including HRs, were expressed with a ratio of <1.0 indicating that the outcome was better in the intervention group compared to the control group.

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/).

Synthesizing the Evidence

Meta-analysis was not planned owing to the lack of a sufficient number of RCTs on this topic.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed.

RESULTS

Search for Systematic Reviews

A search for systematic reviews uncovered 115 documents. Of these, 22 underwent full-text review and none met our pre-planned inclusion criteria; therefore, none were retained (Figure 4-1). There are two older Cochrane guidelines regarding HAI for CRC liver metastases from 2006 and 2009; however, these did not meet the currency criteria. Moreover, Cochrane reviews are not based on systematic reviews, so they do not meet the stated inclusion criteria.

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 633 hits. Of these, 91 underwent a full-text review and 23 [1,3,4,6-25] were retained. A further two papers were identified by study authors and were retained [2,5]. 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.

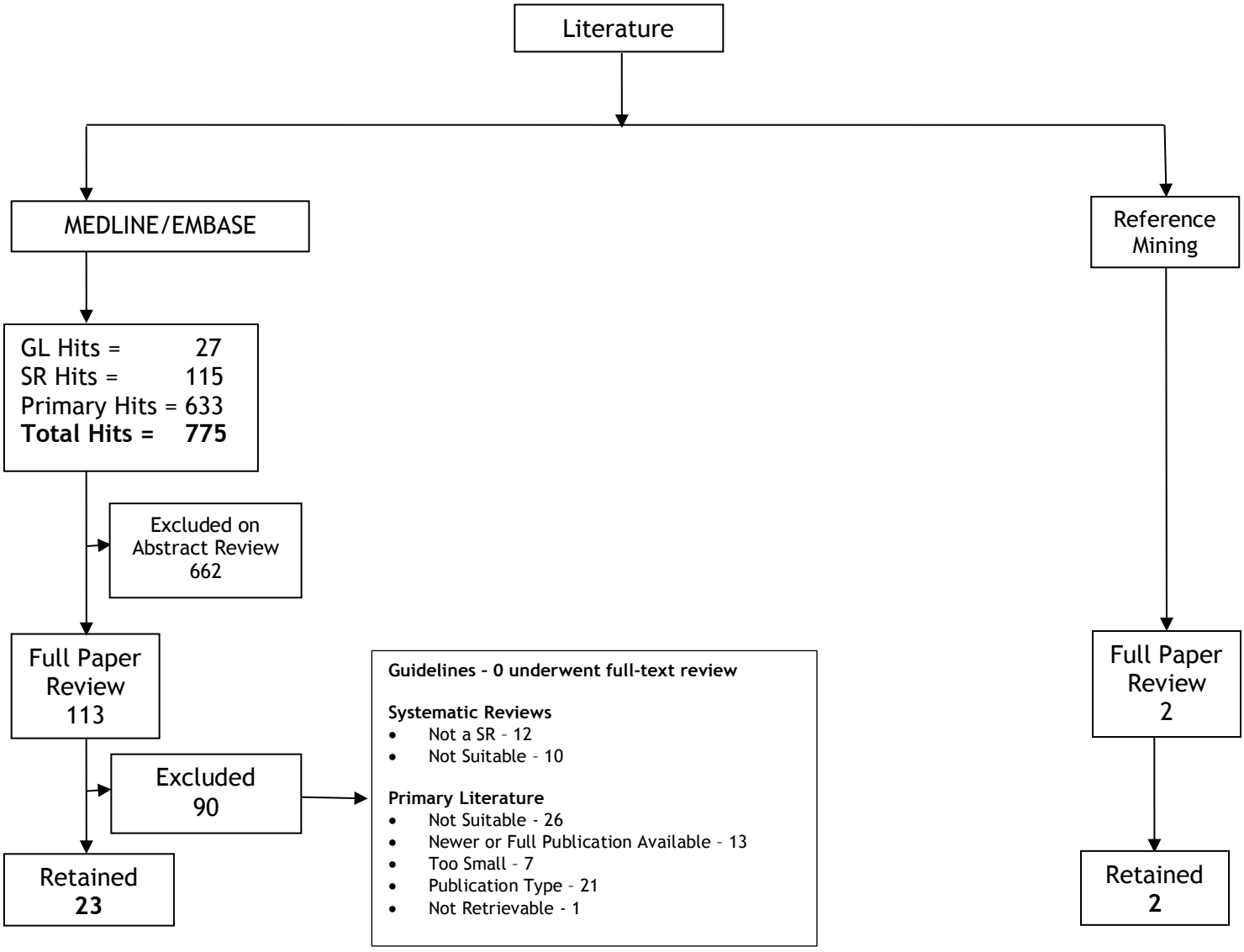

Table 4-1. Studies selected for inclusion

QUESTION	Studies (Papers) retained	References
1 HAI + systemic treatment vs. systemic treatment alone in patients with resectable or resected CRC liver metastases	9 (10)	[1-10]
2. HAI + systemic treatment vs. systemic treatment alone as 1st line treatment in patients with unresectable CRC liver metastases	4 (4)	[11-14]
3. HAI ± systemic treatment vs. systemic treatment alone or BSC alone as 2nd line treatment in patients with unresectable CRC liver metastases	10 (11)	[15-25]

Abbreviations: BSC=best supportive care; CRC=colorectal cancer; HAI=hepatic arterial infusion

Certainty of the Evidence

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).

RCTs

Two RCTs [1-3] presented in three publications 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). The randomized trial by Kemeny et al. [1,2] was assessed to have a low risk of bias for attrition bias, reporting bias and other forms of bias. There was insufficient information about the sequence generation process and the method used for allocation concealment to permit a judgement on selection bias. Unclear risk of bias may simply be a consequence of incomplete reporting but that is unknown. This trial was assessed as having a high risk of bias with respect to performance bias, which measures blinding of participants and personnel. It would not be possible to blind in this study because patients and physicians would know if an HAI pump was inserted (Table 4-2). This was an unusual trial in that the final analysis with longer follow-up data was published in the form of a Letter to the Editor [2]. The Kusano et al. trial [3] scored similarly to the Kemeny et al. [1,2] trial with respect to risk of bias. However, it also had an additional high risk of bias because the trial was closed early for slow accrual. Only 44 of the needed 280 participants were randomized leaving this trial severely underpowered.

Non-RCTs

This guidance document includes 10 non-RCTs [4-11,15,16] that were each assessed using Risk of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/) (Table 4-3). These studies included two prospective [4,11] and six retrospective [5-10,15,16] comparative studies. All the studies except one were judged to have moderate risk for bias due to confounding. There was insufficient information to determine if there was bias due to departures from the intended interventions. With respect to bias in measurement of outcomes, there was low risk of bias for mortality and survival but no information regarding measurement of the other outcomes in each of the studies. The results were consistent across the studies, but the results suffer from indirectness owing to the differences in chemotherapy regimens used in each of the studies and

imprecision due to low patient numbers. Overall, each of the included comparative studies was evaluated to have a high risk of bias.

Phase II Single-Arm Studies

This guidance document includes 11 phase II single-arm studies published in 12 papers [12-14,17-25]. 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
Resected CRC Liver Metastases								
HAI + ST vs. ST	Kemeny et al. 1999, 2005 [1,2]	Unclear	Unclear	High	Unclear	Low	Low	Low
	Kusano et al. 2018 [3]	Low	Unclear	High	Unclear	Low	Low	High

Abbreviations: CRC=colorectal cancer; HAI=hepatic arterial infusion; ST=systemic treatment

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 classification 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
Resected CRC Liver Metastases										
HAI + ST vs. ST	Kusunoki et al. 2000 [4]	Mod	Low	Low	NI	Low	See below[a]	Low	NI	High
	House et al. 2011 [5]	Mod	Low	Low	NI	Low	See below[a]	Low	NI	High
	Goéré et al. 2013 [6]	Mod	Low	Low	NI	Low	See below[a]	Low	NI	High
	Groot Koerkamp et al. 2017 [7]	High	Low	Low	NI	Low	See below[a]	Low	Low	High
	Boerner et al. 2018 [8]	Mod	Low	Low	NI	Low	See below[a]	Low	NI	High
	Gholami 2020 [9]	High	Low	Low	NI	Low	See below[a]	Low	Low	High
	Gholami 2020b [10]	High	Low	Low	NI	Low	See below[a]	Low	Low	High
Unresectable CRC Liver Metastases - 1st LineTreatment										
HAI + ST vs. ST	Li et al. 2016 [11]	Mod	Low	Low	NI	Low	See below[a]	Low	Low	High
Unresectable CRC Liver Metastases - 2nd LineTreatment										
HAI ± ST vs. ST or BSC	Qiang et al. 2015 [15]	Mod	Low	Low	NI	Low	Low	Low	NI	High
	Dhir et al. 2017 [16]	Mod	Low	Low	NI	Low	See below[a]	Low	NI	High

Abbreviations: BSC=best supportive care; CRC=colorectal cancer; HAI=hepatic arterial infusion; Mod=moderate; NI=no information; ST=systemic treatment

[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 HAI to ST in patients with resectable or resected CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

Six studies in seven publications compared HAI plus ST with ST alone in the adjuvant setting [1-6,8], one study investigated the perioperative setting [7] in patients who had undergone resection of CRC liver metastases from the large Memorial Sloan Kettering Cancer Center (MSKCC) liver resection database, and two studies [9,10] reviewed subset populations from the MSKCC database. Five of these studies [1-5] included only patients with liver metastases, one study also included patients with extrahepatic metastases [6], three studies included patients with completely resected extrahepatic disease diagnosed before or at the time of liver resection [7,9,10] and one study, which is only available in abstract form, did not report this information [8]. Survival outcomes are presented in Table 4-4.

Results from the Kemeny et al. randomized trial [1,2] demonstrated a significant increase in OS at two years for adjuvant HAI (floxuridine [FUDR]) plus ST (5-fluorouracil [5-FU]) as compared with ST (5-FU) alone (86% vs. 72%, p=0.03); however, a significant difference in the median OS between the two groups was not observed (68.4 vs. 58.8 months, respectively, p=0.10) (Table 4-4). A multivariate analysis of overall mortality at two years indicated an adjusted relative risk (RR) for death of 0.43 (95% confidence interval [CI], 0.20 to 0.91; p=0.027) among patients treated with adjuvant HAI plus ST, as compared with those who received ST alone. Furthermore, both the overall PFS (31.3 vs. 17.2 months, p=0.02) and survival free of hepatic progression (not reached vs. 32.5 months, p<0.01) were significantly greater in the adjuvant HAI plus ST group than in the ST-alone group. Similarly, the adjusted RR for overall (0.59, 95% CI, 0.37 to 0.93; p=0.025) and hepatic (0.19, 95% CI, 0.08 to 0.42, p<0.001) progression at two years both favoured adjuvant HAI plus ST. The Kusano et al. trial [3] reported no significant differences between the trial arms [HAI(5-FU) plus ST(UFT) vs. ST(UFT)] for any of the outcomes measured; three-year OS, three-year DFS, and three-year hepatic DFS. Unfortunately, only 44 of an expected 280 participants were enrolled and randomized, and this trial was terminated early for slow accrual; therefore, this trial was severely underpowered to detect any differences between the trial arms.

Among the comparative studies, Kusunoki et al. [4] reported a significantly improved OS at five years for adjuvant HAI (5-FU) plus ST (UFT) as compared with ST (UFT) alone (59% vs. 27%, p=0.00001), whereas Goere et al. [6] did not demonstrate a significant difference between the two groups (54% vs. 52%, respectively, p=0.34). House et al. [5] reported the disease-specific survival (DSS) at five years. Adjuvant HAI (FUDR) plus ST (5-FU+oxaliplatin+irinotecan) was shown to have a significant advantage over ST (5-FU+oxaliplatin+irinotecan) alone (75% vs. 55%, p<0.01). The number of liver metastases and use of adjuvant HAI were the only two predictors of DSS in both the univariate and multivariate analyses. Groot Koerkamp et al. [7] also reported a significant five-year OS advantage for HAI (FUDR) plus ST (various systemic therapies) compared to ST (various systemic therapies) alone (52.9% vs. 37.9%, p<0.001). Patients who received perioperative HAI plus ST had significantly longer OS than those who received ST alone (67 vs. 44 months, p<0.001). The patients in the two arms of this study differed significantly on almost all clinical and pathologic characteristics measured. To adjust for this, the authors did a propensity score analysis. The adjusted HR also showed a benefit for perioperative HAI plus ST (0.67; 95% CI, 0.59 to 0.76; p<0.001) [7]. Gholami et al. [9] studied a subset of patients from the MSKCC database for whom KRAS mutational status was known. They report significant five-year OS advantage for HAI (FUDR) plus ST (various systemic therapies) compared to ST (various systemic therapies) alone for both the KRAS wild-type (76% vs. 57%, p<0.001) and KRAS mutated (59% vs. 40%, p<0.001) subgroups. Gholami et al. [10]

studied another subset of patients from the MSKCC database for whom laterality of primary tumour was known. They report significant five-year OS advantage for HAI (FUDR) plus ST (various systemic therapies) compared to ST (various systemic therapies) alone for both left-sided (73% vs. 55%, p<0.01) and right-sided (68% vs. 45%, p<0.01) primary tumours.

Despite not demonstrating a significant difference in OS between adjuvant HAI plus ST and ST alone, Goere et al. [6] did show a significantly longer DFS at three years for patients in the adjuvant HAI plus ST arm (33% vs. 5%, p<0.0001). Kusunoki et al. [4] also reported a similar benefit in DFS for adjuvant HAI plus ST (32.0 vs.16.2 months, p=0.0004). In the studies that reported recurrence-free survival (RFS), adjuvant HAI plus ST was associated with improved overall RFS in the House et al. [5] two-arm (48% vs. 25%, p<0.01) and the Beorner et al. [8] three-arm study (1.8 years vs. 1.2 years vs. 1.4 years, p=0.02) studies. Five-year RFS was also significantly better in the HAI plus ST arm in Gholami et al. [10] but only for those with left-sided primary tumours. Hepatic recurrence, whether reported as hepatic DFS or hepatic RFS was significantly longer in those who received HAI plus ST compared to ST alone in all comparative studies that reported this outcome [4-6] (Table 4-4).

Five of the nine studies reported toxicity and/or complications [1-6] (Table 4-5). In the Kemeny et al. randomized study [1,2], the rates of adverse effects of at least moderate severity were similar in both groups (reporting neutropenia, vomiting, nausea, and stomatitis) except for diarrhea, which occurred more frequently in the adjuvant HAI plus ST group (29% vs. 14%). Hospitalization owing to diarrhea, leukopenia, mucositis, or small bowel obstruction was also more common in the adjuvant HAI plus ST group (39% vs. 22%, p=0.02). There were 16 additional complications (22%) related to the pump or catheter among the 74 patients randomized to HAI plus ST (infection, hepatic arterial thrombosis, dislodged catheters, pseudoaneurysm of the hepatic artery, perfusion to areas outside the liver). In the Kusano et al. trial [3] the frequency of grade 3 or greater adverse events was small and there were no significant differences between the trial arms. In the Kusunoki et al. [4] study, three patients (10%) treated with adjuvant HAI plus ST developed grade 3 toxicity (one had nausea/emesis; two had back pain) and only one patient (3%) developed catheter-related pseudoaneurysm. No grade 3 or higher adverse events were observed in the ST-alone group. House et al. [5] also reported HAI pump-related complications in four patients (3%); two cases of arterial pseudoaneurysm, two cases of gastrointestinal ulceration, and one case of biliary sclerosis. The rates of postoperative complications were similar in the two groups (25% for adjuvant HAI plus ST versus 20% for ST alone, p=0.11). In the Goere et al. [6] study, adjuvant HAI plus ST was discontinued because of toxicity in eight patients (18%) and catheter dysfunction in six patients (14%).

Table 4-4. Results of the studies evaluating the benefits of the addition of HAI to systemic therapy compared to systemic therapy alone in patients with resected CRC liver metastases

STUDY	STUDY TYPE	STUDY ARMS	HAI Used	ST Used	N	OS	DFS	PFS	hPFS
Kemeny et al. 1999, 2005 [1,2]	RCT	HAI + ST ST	FUDR + Dex + Heparin + Saline	5-FU + LV	74 82	**Median (mos)** 68.4 58.8 p=0.10 **2 year** 86% 72% p=0.03		**Median (mos)** 31.3 17.2 p=0.02 **2 year** 57% 42% p=0.07	**Median hPFS (mos)** not reached 32.5 p<0.01 **2 year** 90% 60% p<0.001
Kusano et al. 2018 [3]	RCT	HAI + ST ST	5-FU	UFT + LV	22 22	**3 year** 80.2% 85.2% p=0.192	**3 year** 43.5% 58.0% p=0.534	NR	**3-year hDFS** 62.8% 76.8% p=0.491
Kusunoki et al. 2000 [4]	Prosp	HAI + ST ST	5-FU	UFT	30 28	**3 year** 74% 32% p=NR **5 year** 59% 27% p=0.00001	**Median (mos)** 32.0 16.2 p=0.0004	NR	**Median hRFS (mons)** 34.2 18.4 p=0.00002
House et al. 2011 [5]	Retro	HAI + ST ST	FUDR + Dex	5-FU + LV + oxaliplatin + irinotecan	125 125	**3-year DSS** 86% 76% p<0.01 **5-year DSS** 75% 55% p<0.01	**NR**	5-year RFS 48% 25% p<0.01	**5-year hRFS (mons)** 79% 55% p<0.001

Goéré et al. 2013 [6]	Retro	HAI + ST ST	Oxaliplatin + 5-FU + LV	FOLFOX or FOLFIRI	44 54	**3 year** 75% 62% p=0.17 **5 year** 54% 52% p=0.34	**3 year** 33% 5% p<0.0001	NR	**3-year hDFS** 49% 21% p=0.0008
Groot Koerkamp et al. 2017 [7]	Retro	HAI + ST ST	FUDR	Varied over time; at discretion of treating medical oncologist	785 158 3	**Median (mos)** 67 44 p<0.001 **5 year** 52.9% 37.9% p<0.001	NR	NR	NR
Beorner et al. 2018 [8] abstract	Retro	HAI + ST ST No treatment	NR	NR	79 77 84	**Median (yr)** 6.2 4.0 4.1 p<0.01	**NR**	**Median RFS (yr)** 1.8 1.2 1.4 p=0.02	NR
Gholami et al. 2020 [9]	Retro	**KRAS-WT** HAI + ST ST **KRAS-MUT** HAI + ST ST	FUDR + Dex + Heparinized Saline	At the discretion of the treating medical oncologist	235 183 131 125	**5 year** 76% 57% p<0.001 59% 40% p<0.001	**NR**	**NR in this format**	NR

Gholami et al. 2020 [10]	Retro	**LCC** HAI + ST ST **RCC** HAI + ST ST	FUDR + Dex + Heparinized Saline	At the discretion of the treating medical oncologist	 192 113 83 99	**5 year** 73% 55% p<0.01 68% 45% p<0.01 interaction = ns	**NR**	**5 year** 34% 22% p=0.038 33% 29% p=0.65 interaction = ns	NR

Abbreviations: Dex=dexamethasone; DFS=disease-free survival; DSS=disease-specific survival; FOLFIRI=fluorouracil;leucovorin/irinotecan; FOLFOX=fluorouracil/leucovorin/oxaliplatin; 5-FU=fluorouracil; FUDR=floxuridine; HAI=hepatic arterial infusion; hDFS=hepatic disease-free survival; hPFS=hepatic progression-free survival; hRFS=hepatic recurrence-free survival; LCC=left colon cancer; LV=leucovorin; mos=months; MUT=mutated; NR=not reported; ns=not significant; OS=overall survival; Prosp=prospective; RCC=right colon cancer; RCT=randomized controlled trial; Retro=retrospective; ST=systemic therapy; UFT=uracil+tegafur; WT=wild type; yr=year

Table 4-5. Toxicity results of the studies evaluating the benefits of the addition of HAI to systemic therapy compared to systemic therapy alone in patients with resected CRC liver metastases

STUDY	STUDY TYPE	STUDY ARMS	N	HAI PUMP-RELATED COMPLICATIONS (N)	≥GRADE 3 ADVERSE EVENTS (%) HAI+ST vs. ST alone
Kemeny et al. 1999, 2005 [1,2]	RCT	HAI + ST ST	74 82	Clots of hepatic artery – 2 Infections of pump pocket – 6 Complications related to pump or catheter - 16	≥ Moderate Adverse Events Neutropenia – 18 vs. 21, p=NR Diarrhea - 29 vs. 14, p=NR Vomiting – 10 vs. 5, p=NR Nausea – 13 vs. 4, p=NR Stomatitis – 11 vs. 9, p=NR Hospitalization Because of Adverse Events – 39 vs. 22, p=0.02
Kusano et al. 2016 [3]	RCT	HAI + ST ST	22 22	NR	Small number of ≥ grade 3 adverse events and there were no significant differences in the study arms
Kusunoki et al. 2000 [4]	Prosp	HAI + ST ST	30 28	1 case of catheter-related pseudoaneurysm 2 cases of catheter-related complications	10 vs 0
House et al. 2011 [5]	Retro	HAI + ST ST	125 125	4 cases of pump-related complications	Postoperative complications – 25 vs 20, p=0.11
Goéré et al. 2013 [6]	Retro	HAI + ST ST	44 54	HAI + ST discontinued because of: Catheter Dysfunction – 6(14%)	HAI + ST discontinued because of: Toxicity – 8 (18%)
Groot Koerkamp et al. 2017 [7]	Retro	HAI + ST ST	1583 785	NR	NR
Boerner et al. 2018 [8] *abstract*	Retro	HAI + ST ST No treatment	79 77 84	NR	NR
Gholami et al. 2020 [9]	Retro	HAI + ST ST	366 308	NR	NR
Gholami et al. 2020 [10]	Retro	HAI + ST ST	275 212	NR	NR

Abbreviations: HAI=hepatic arterial infusion; NR=not reported; RCT=randomized controlled trial; Retro=retrospective; ST=systemic therapy

Question 2: What is the benefit of the addition of HAI to ST in first-line treatment in patients with unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

One non-randomized study comparing HAI plus ST with ST alone as a first-line treatment for elderly patients with unresectable CRC liver metastases and no detectable extrahepatic metastatic disease was retained [11]. Results demonstrated that HAI (FUDR) plus ST (capecitabine) was associated with a prolonged median OS (18.5 vs. 13 months, p=0.0312) (Table 4-6). The most common grade 3 adverse events were nausea/vomiting (16.7% for HAI plus ST vs. 7.4% for ST alone), abdominal pain (16.7% vs. 11.1%, respectively), alanine aminotransferase/aspartate aminotransferase elevation (12.5% vs. 3.7%, respectively), hand and foot syndrome (12.5% vs. 14.8%, respectively), and diarrhea (12.5% vs. 3.7%, respectively); in all cases, the adverse events were reversible and no patients discontinued HAI therapy due to complications related to the catheter, port, or pump.

Given the paucity of comparative data for this question, three phase II single-arm studies of HAI plus ST were retained [12-14]. Fallik [12] enrolled 75 participants. HAI (pirarubicin) plus ST (5-FU) achieved median survival of 19 months (95% CI, 15 to 22 months) and a median time to hepatic progression of 8.3 months (95% CI, 5.6 to 14.3 months) (Table 4-6). Objective response rate (ORR) was 31.9%, consisting of one complete response and 21 partial responses. The most common grade 3/4 clinical toxicities were nausea and vomiting (11%), alopecia (19%), and diarrhea (10%). The most common grade 3/4 hematological toxicities were neutropenia (52%) and anemia (17%).

Idelevich et al. [13] studied HAI plus ST (irinotecan plus 5-FU) in 31 participants. Median OS was 36 months (95% CI, 25 to 39 months) and median TTP was 12 months (95% CI, 8 to 16 months). ORR was 65%, consisting entirely of partial responses. Nine patients (29%) were subsequently able to have surgery with curative intent. The most common grade 3/4 toxicities were diarrhea (13%) and neutropenia (10%).

Chen et al. [14] studied HAI plus ST (irinotecan + oxaliplatin + FUDR plus 5-FU) in 31 participants. Median OS was 24.8 months (range, 7 to 46 months) and median TTP was 10.1 months (range, 1 to 18 months). ORR was 61.3%, consisting entirely of partial responses. The most common grade 3/4 toxicities were vomiting (90.3%) and elevated serum transaminases (19.4%).

Table 4-6. Results of the studies evaluating the benefits of the addition of HAI to systemic therapy compared to systemic therapy alone in those with unresectable CRC liver metastases

STUDY	STUDY TYPE	STUDY ARMS	HAI Used	ST Used	N	MEDIAN OS (months)	MEDIAN DFS (months)	MEDIAN PFS (months)	MEDIAN hPFS (months)
UNRESECTABLE – FIRST-LINE TREATMENT- Comparative Study									
Li et al. 2016 [11]	Prosp	HAI + ST ST	FUDR	Capecitabine	24 27	18.5 13.0 p=0.0312	NR	NR	NR
UNRESECTABLE – FIRST-LINE TREATMENT- Single Arm Phase II Study									
Fallik et al. 2003 [12]	Prosp	HAI + ST	Pirarubicin	5-FU + LV	75	19	NR	NR	Median TTHP 8.3
Idelevich et al. 2009 [13]	Prosp	HAI + ST	Irinotecan + LV + 5-FU	UFT +LV	31	36	NR	Median TTP 12	NR
Chen et al. 2012 [14]	Prosp	HAI + ST	Irinotecan + oxaliplatin + FUDR	5-FU + LV	31	24.8	NR	Median TTP 10.1	NR

Abbreviations: 5-FU=fluorouracil; CRC=colorectal cancer; DFS=disease-free survival; FUDR=floxuridine; HAI=hepatic arterial infusion; hPFS=hepatic progression-free survival; LV=leucovorin; NR=not reported; OS=overall survival; PFS=progression-free survival; Prosp=prospective; RCT=randomized controlled trial; ST=systemic therapy; TTHP=time to hepatic progression; TTP=time to progression; UFT=uracil + tegafur

Question 3: What is the benefit of HAI with or without ST in second-line (or later) treatment of patients with unresectable CRC liver metastases with respect to OS, DFS, PFS, and hepatic PFS?

Two studies compared HAI plus ST with ST alone as second-line or later treatment for patients with unresectable CRC liver metastases [15,16] (Table 4-7). In the Qiang et al. [15] retrospective study, median survival was significantly longer for HAI (5-FU) plus ST (various systemic therapy regimens) versus ST (various) alone (19.8 vs. 9.0 months, p=0.045), as was median overall PFS (5.7 vs. 3.0 months, p=0.02) and hepatic PFS (8.1 vs. 4.7 months, p=0.027). Grade 3/4 hematological toxicity occurred in two patients (10%) treated with HAI plus ST and in two patients (8.7%) treated with ST alone. There was one patient (4.3%) in the ST-alone group who developed graded 3/4 hepatic toxicity. HAI catheter-related complications were documented in two patients (10%). In the Dhir et al. retrospective case-control study [16], median survival was significantly longer for HAI (FUDR) plus ST ("modern" systemic therapy) versus ST ("modern" systemic therapy) alone (32.8 months vs. 15.3 months, p<0.0001). Toxicity data were not provided.

Given the paucity of comparative data for this question, nine phase II single-arm publications representing eight trials were retained [17-25]. Of these eight trials, two studied HAI without systemic therapy in second-line treatment of those with unresectable CRC liver metastases [17,18]. The Patt et al. [17] study consisted of 48 participants receiving HAI alone (rIFN-α2b + 5-FU). ORR was 33.3% among the 45 evaluable participants. The most common grade 3/4 toxicities were granulocytopenia (42%), mucositis (40%), and thrombocytopenia (12%). The Sato et al. [18] study was larger and consisted of 137 participants who received HAI alone (5-FU). Median OS was 4.8 months and time to treatment failure was 2.4 months. Grade 3/4 toxicities occurred in four (2.9%) patients.

The remaining seven publications representing six single-arm phase II trials studied HAI with ST in second-line treatment [19-25] (Table 4-7). The Zelek et al. [19] study included 31 participants. Pirarubicin was used for HAI and irinotecan plus 5-FU was used for systemic therapy. ORR was 48%, consisting entirely of partial responses. Liver resection was achieved in 11 (35%) patients. Median OS was 20.5 months for the overall sample. However, median OS was not reached in those who subsequently had a R0 resection and was 13.9 months for all others. Whereas median PFS was 9.1 months for the entire sample, median PFS was 20.2 months versus 4.2 months in those who subsequently had a R0 resection and those who did not. Grade 3/4 neutropenia was experienced by 77% of participants.

Kemeny et al. [20] enrolled 63 participants; 26 for first-line treatment (not reported here) and 37 for second-line treatment. FUDR was used for HAI and mitomycin C was used for systemic therapy. ORR was 70.3% and median survival was 20 months. Toxicity data were not parsed out by first- and second-line participants.

Boige et al. [21] studied HAI plus ST in 44 participants. Oxaliplatin was used for HAI and 5-FU was used for systemic therapy. In the 30 patients who were evaluable ORR was 62%, consisting entirely of partial responses. ORR for the intent-to-treat population was 55%. Seven participants were able to go on to R0 resection and one participant was able to have radiofrequency ablation of their liver metastases. Median OS was 16.0 months and median PFS was 7.0 months. The most common grade 3/4 toxicities were neutropenia (44%), neuropathy (16%), and abdominal pain (14%).

The OPTILIV study enrolled 64 participants [22,23]. Participants were categorized as early (within 3 courses) and late responders (more than 3 courses). HAI consisted of irinotecan, oxaliplatin and 5-FU. Systemic therapy was cetuximab. Overall ORR in the 57 evaluable participants was 45.6% or 26 participants; 16 were early responders and 10 were late responders [22]. ORR for the entire sample was 40.6% [23]. Seventeen participants underwent complete

liver metastases resection. Seven (43.8%) of early responders subsequently underwent R0 or R1 surgery. Median OS in early and late responders was 35.1 months and 20.2 months respectively (p=0.01, log rank) [22]. Overall, median OS and PFS for the intent-to-treat population were 25.7 months and 9.3 months, respectively. Median OS was significantly greater in those who subsequently had liver metastases resected compared to those who did not have liver metastases resected (35.2 months vs. 18.7 months, p<0.001). Median PFS was significantly greater in those who subsequently had liver metastases resected compared to those who did not have liver metastases resected (15.7 months vs. 8.6 months, p<0.001) [23]. The most common grade 3/4 toxicities among the 57 evaluable participants were neutropenia (46%), abdominal pain (28%), leukopenia (26%), fatigue (19%), diarrhea (18%), and nausea (11%) [22].

Boilève et al. [24] studied HAI plus ST plus targeted therapy (TT) in 89 participants. HAI consisted of oxaliplatin, ST consisted of LV5FU2 or FOLFIRI and TT consisted of cetuximab or panitumumab or bevacizumab. ORR was 42% and consisted of one complete and 36 partial responses. Median OS was 20 months and median PFS was nine months. Grade 3/4 toxicities were experienced by 79% of participants. The most common grade 3/4 toxicities were neutropenia (40%), abdominal pain during HAI administration (43%), and neurotoxicity (12%).

Muaddi et al. [25] studied HAI plus ST in 154 participants. HAI consisted of FUDR and ST was at the discretion of the treating medical oncologist. ORR was 56.5% and median OS was 19.5 months. One-year PFS was 33.1% and three-year PFS was 4.1%. Non-HAI pump complications occurred in 33.8% of participants and HAI pump complications occurred in 14.3% of participants.

Table 4-7. Results of the studies evaluating the benefits of the addition of HAI to systemic therapy compared to systemic therapy alone in patients with unresectable CRC liver metastases

STUDY	STUDY TYPE	STUDY ARMS	HAI Used	ST Used	N	MEDIAN OS (months)	MEDIAN DFS (months)	MEDIAN PFS (months)	MEDIAN hPFS (months)
UNRESECTABLE – SECOND-LINE TREATMENT- Comparative Studies									
Qiang et al. 2015 [15]	Retro	HAI + ST ST	5-FU + Dex + heparin + saline	Depended on what ST regimens had been previously administered	20 23	19.8 9.0 p=0.045	NR	5.7 3.0 p=0.02	8.1 4.7 p=0.027
Dhir et al. 2017 [16]	Retro	HAI + ST ST	FUDR	"Modern" systemic chemotherapy	40 46	32.8 15.3 p<0.0001	NR	NR	NR
UNRESECTABLE – SECOND-LINE TREATMENT- Single-Arm Phase II Studies									
Patt et al. 1997 [17]	Prosp	HAI	rIFN-α2b + 5-FU + Dex	NA	48	NR	NR	NR	NR
Sato et al. 2020 [18]	Retro	HAI	5-FU	NA	137	4.8	NR	TTF 2.4	NR
Zelek et al. 2003 [19]	Prosp	HAI + ST	Pirarubicin	Irinotecan + 5-FU + LV	31	20.5	NR	9.1	NR
Kemeny et al. 2005 [20]	Prosp	HAI + ST	FUDR + Dex	Mitomycin C	37	20	NR	NR	NR
Boige et al. 2008 [21]	Prosp	HAI + ST	Oxaliplatin	5-FU + LV	44	16.0	NR	7.0	NR
OPTILIV 2016 [22,23]	Prosp	HAI + ST	Irinotecan + oxaliplatin + 5-FU	cetuximab	64	25.7	NR	9.3	NR

Boilève et al. 2020 [24]	Retro	HAI + ST+TT[a]	Oxaliplatin	LV5FU2 or FOLFIRI	89	20	NR	9	NR
Muaddi et al. 2020 [25]	Retro	HAI + ST	FUDR + heparinized saline + Dex	At the discretion of treatment medical oncologist	154	19.5	NR	1-yr – 33.1% 3-yr – 4.1%	NR

[a]**TT was cetuximab, panitumumab or bevacizumab**

Abbreviations: 5-FU=fluorouracil; Dex=dexamethasone; DFS=disease-free survival; FUDR=floxuridine; HAI=hepatic arterial infusion; hPFS=hepatic progression-free survival; LV=leucovorin; NR=not reported; OS=overall survival; PFS=progression-free survival; Prosp=prospective; RCT=randomized controlled trial; Retro=retrospective; ST=systemic therapy; TT=targeted therapy; TTF=time to treatment failure

Ongoing, Unpublished, or Incomplete Studies

Study of Systemic Chemotherapy With/Without HAI in Patients with Initially Unresectable Colorectal Liver Metastasis	
Protocol ID:	NCT02102789
Date last modified:	October 29, 2019
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	RO resection rates
Accrual:	142 will be accrued
Sponsorship:	Yuhong Li, Sun Yat-sen University
Status:	Recruiting
Study Comparing HAI Plus Chemotherapy and Chemotherapy Alone in Patients With Unresectable CRLM	
Protocol ID:	NCT03125161
Date last modified:	April 24, 2017
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Conversional resection rates
Accrual:	150 will be accrued
Sponsorship:	Fudan University
Status:	Recruiting
Hepatic Arterial Infusion With Floxuridine and Dexamethasone Combined With Combination Chemotherapy in Treating Patients With Colorectal Cancer That Has Spread to the Liver	
Protocol ID:	NCT00492999
Date last modified:	February 5, 2021
Type of trial:	Non-randomized study, parallel assignment, active control, open label
Primary endpoint:	Resectability rate
Accrual:	64 will be accrued
Sponsorship:	Memorial Sloan Kettering Cancer Center; National Cancer Institute
Status:	Active, not recruiting
FUDR/Oxaliplatin HAI Plus Irinotecen vs. FOLFOXIRI Chemotherapy in Treating Initially Unresectable CRCLM	
Protocol ID:	NCT03678428
Date last modified:	October 29, 2012
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Overall response rate
Accrual:	160 will be accrued
Sponsorship:	Yuhong Li, Sun Yat-sen University
Status:	Not yet recruiting
Improving Surgery of Liver Metastases: a Trial of the Arterial Chemotherapy Network (SULTAN)	
Protocol ID:	NCT03164655
Date last modified:	June 26, 2020
Type of trial:	Randomized study, parallel assignment, active control, double blind
Primary endpoint:	Curative intent (R0-R1) resection rate and/or ablation rate
Accrual:	140 will be accrued
Sponsorship:	UNICANCER
Status:	Recruiting

DISCUSSION

Significant advances have been achieved over the past 25 to 30 years in the management of metastatic CRC. The current estimated median survival for patients with metastatic CRC is 30 months or more, which is more than double the 12–15-month survival rates quoted 25 years ago [39-42]. Today there are more options both in the types of systemic chemotherapy available and treatment choices in later lines of therapy, contributing substantially to improved survival rates. We await emerging survival data incorporating newer targeted therapies and immune checkpoint inhibitors as an additional systemic therapy option in metastatic CRC [22].

Surgical resection, ablation and external beam radiotherapy techniques are routinely incorporated in the management of suitable patients with limited metastatic CRC, and these techniques have also advanced. Several other techniques for liver-directed regional therapies, including conventional transarterial chemoembolization (TACE), drug-eluting bead-TACE, or transarterial radioembolization and HAI, have been developed. A recently published companion OH (CCO) Guideline addresses the evidence for the other liver-directed regional therapies [2-30a: Regional Therapies for Colorectal Cancer Liver Metastases https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/63286]. In this guideline we set out to critically appraise the evidence for HAI.

In principle, HAI takes advantage of providing chemotherapy directly thorough the hepatic artery, which is the almost exclusive blood supply for CRC hepatic metastases. An implantable device, typically a hepatic artery infusion pump, is surgically implanted subcutaneously, and through its attached catheter can deliver an intravenous chemotherapeutic directly into the hepatic artery. The specific fluoropyrimidine used is called FUDR, which has a high liver extraction rate. It is delivered at a continuous infusion rate rather than intermittent, which is deemed to allow more efficient drug exposure to the cancer. HAI therapy mandates a collaborative multidisciplinary team.

HAI has not been widely adopted as a standard liver-directed therapy in metastatic CRC management, this despite the first randomized HAI trial having been published over 20 years ago. This guideline analyzed the evidence for the role of HAI in combination with systemic chemotherapy in resected or resectable liver metastatic disease, and its role with or without chemotherapy in the metastatic setting.

Our literature review dating back to 1990 identified only two RCTs, plus eight comparative or phase II trials. Both RCTs were in the setting of resected or resectable liver metastatic disease. The landmark Kemeny et al. [1,2] trial was a single-institution study published over 20 years ago. Despite the trial demonstrating statistical significance in one of its two primary endpoints, the trial did not lead to more widespread adoption of HAI, nor have subsequent randomized clinical trials been completed. Consequently, it is difficult to interpret results of this trial in the modern era of liver-only metastatic CRC management; this would require randomized trials incorporating contemporary comparator arms. The Kusano et al. 2018 [3] trial closed early, with only 44 of the planned 280 patients accrued over two-and-a-half years; interpretation of results is thus very limited. There is also a paucity of evidence to ascertain the relative benefits versus harms, or associated impact on QOL, in comparison to contemporarily available local and systemic treatments. Selection bias in these studies also limits generalizability. The Working Group members found insufficient evidence to support the use of HAI outside of a clinical trial.

The evidence in first-line or later setting for patients with unresectable liver metastatic disease included only a handful of small comparative, single-arm and retrospective studies. The Working Group members concluded that the addition of HAI to ST is not recommended outside of a clinical trial.

On a practical level, despite evidence for HAI having been available for over 20 years, there has been minimal uptake of HAI technology. Hence, the expertise for HAI techniques,

including implantation and maintenance of arterial ports or pumps to allow safe bolus or infusion delivery of drugs and expertise of chemotherapy delivery, is restricted to a very small number of highly specialized centres and individuals. There are unique complications and toxicities that are not well understood outside of these few specialty centres across North America. Availability of the reference chemotherapy drug FUDR is very limited and FUDR is not a commercially approved drug in Canada. Only one cancer centre in Ontario has some expertise in the use of HAI, with its program limited to a single-institution phase II single arm trial for which Health Canada provided special permission to use FUDR. Information regarding this trial can be found at: https://www.canadiancancertrials.ca/Trial/detail.aspx?TrialId=ON1233&lang=en. Moreover, there has been a paucity of ongoing high-quality research that would support the ongoing development of HAI in the contemporary context of systemic and local therapies used in metastatic disease.

There may be subsets of patients for whom HAI may be of benefit. In combination with modern systemic therapy, HAI may be beneficial in the first-line setting as an adjunct to improve response in patients who are responding or have stability of their liver-only metastases on systemic chemotherapy. This strategy may also result in a subset of patients being converted to having resectable disease. The use of HAI in this setting should be conducted in a clinical trial or in a prospectively acquired database or research protocol.

CONCLUSIONS

There is insufficient evidence to support the use of HAI in the treatment of CRC. The addition of HAI to systemic therapy in resectable or resected CRC liver metastases is not recommended outside of a modern clinical trial. The addition of HAI to systemic therapy in the first-line or later setting cannot be recommended outside of a modern clinical trial.

Hepatic Arterial Infusion for Colorectal 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 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the six members of the GDG Expert Panel, six members voted, and none abstained, for a total of 100% response in October 2020. Of those who voted, six 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. Remove "outside of a clinical trial" from the recommendations.	We have moved this phrase to the justification for the recommendation section for each recommendation.
2. Expand on how advances in treatment impact the treatment landscape in the Key Evidence for Recommendation 1.	We have made this modification.
3. Include a description of the different methods used to place the HAI catheter.	Information about this was added to the discussion.
4. Rationale for why borderline resectable patients are not included in this guideline.	This population was not covered in the trials we found; therefore, no change was made.
5. Make a recommendation for borderline resectable patients.	This is beyond the scope of this guideline.
6. Provide information on the chemotherapy used in each trial.	This information was added to the tables for each question.
7. Various small editorial changes were suggested.	These changes were made.

RAP Review and Approval

Three RAP members reviewed this document in October 2020. The RAP conditionally approved the document and final approval was given February 24, 2021. 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 RAP

Comments	Responses
1. Include outcomes of interest in the guideline objectives.	Revision made.
2. Include information on the chemotherapy used in the trials.	This information was added to the tables for each question.
3. Why were previous Cochrane guidelines not included in the systematic review?	We have modified the document to acknowledge the existence of these guidelines. However, they were not used as part of the evidence collected because they did not meet the inclusion criteria. Specifically,

	they were too old, and they were not based on a systematic review.
4. Provide more clarity on how systemic therapy has changed since the randomized trials used in the review. This would provide some context for the recommendations.	Modifications were made to the discussion to address this information requested.
5. The comments on "undesirable effects" in the justification section for each recommendation are awkwardly worded.	These sentences were revised.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Two targeted peer reviewers from British Columbia and Missouri who are considered to be clinical and/or methodological experts on the topic were identified by Working Group. Two agreed to be the reviewers (Appendix 2). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.					2
4. Rate the completeness of reporting.				1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	1
6. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					2
8. I would recommend this guideline for use in practice.					2
9. What are the barriers or enablers to the implementation of this guideline report?	Reviewer 1 – Dissemination, education Reviewer 2 - Limited barriers				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers

Comments	Responses
1. Comments received were all positive with no indication for any changes.	We have therefore not made any changes based on targeted peer reviewer comments.

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 those in the PEBC database who have indicated 'gastrointestinal' as an area of interest were contacted by email to inform them of the survey. A total of 120 professionals were contacted, and all but one practice in Ontario. Fourteen stated that they did not have interest in this area or were unavailable to review this guideline at the time. Twelve (11%) responses were received. The results of the feedback survey from 12 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

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

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				7 (58)	5 (42)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			3 (25)	6 (50)	3 (25)
3. I would recommend this guideline for use in practice.			1 (8)	5 (42)	6 (50)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Accessibility and experience with a pump • Lack of modern-day evidence with modern systemic therapy Enablers: • Educating patients (including using this document) on a case-by-case basis on the use of HAI				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants

Comments	Responses
1. A comment that it would be easier to read if we included the chemotherapeutic agents used in the text of the document rather than just in the tables.	This has been added to the text.
2. A comment to clarify whether FUDR is not approved by Health Canada or if it is approved but not marketed.	This has been clarified in the Discussion.
3. A comment that there should be a single registry in Ontario for all patients treated with HAI.	The Working Group agrees but the ability to do so is beyond the scope of this guidance document.

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: Affiliations and Conflict of Interest Declarations

Appendix 1. Members of the Hepatic Arterial Infusion 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

John Lenehan	MO	London Regional Cancer Progam London, 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
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Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, 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 Hepatic Arterial Infusion 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), Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Members of the Heptatic Arterial Infusion for Colorectal Cancer Liver Metastases Working Group

Name	Specialty	Affiliation	Declarations of interest
Jim Biagi Working Group Chair	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Shiva Jayaraman	SO	St. Joseph's Hospital Toronto, ON	Declared they had no conflicts of interest.
Rebecca Wong	RO	Princess Margaret Hospital Toronto, 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; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Hepatic Arterial Infusion for Colorectal Cancer Liver Metastases Guideline Development Group Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Scott Berry	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON	In the past five years has received $500 or more in a single year to act in a consulting capacity for Novartis, Onivyde, Bayer, Amgen and Ipson. In the past five years has received independence education grants from Ipsen (PI on a cognitive study and tumour bank) and Novartis (independent grant and tumour bank).
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Julie Hallet	SO	Odette Cancer Centre Toronto, ON	In the past five years has received $500 or more in a single year for speaking honoraria from Ipsen and Novartis. In the past five years has received unrestricted educational grants from Ipsen, Novartis and Baxter.
Erin Kennedy	SO	Mount Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, ON	In the past 5 years has received $500 or more in a single year to act in a consulting capacity for Novartis and Integra. In the past five

			years has received $500 or more in a single year for other financial support from Bayer. In the past five years has received grant support from Bayer.

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

Members of the Hepatic Arterial Infusion for Colorectal Cancer Liver Metastases Guideline Development Group Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Laurie Elit	SO	Juravinski Cancer Centre	Declared they had no conflicts of interest.
Jonathan Sussman	RO	Juravinski Cancer Centre	Declared they had no conflicts of interest.
Bill Evans	MO	Oncosynthesis Consulting Inc.	Declared they had no conflicts of interest.

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

Members of the Hepatic Arterial Infusion for Colorectal Cancer Liver Metastases Guideline Development Group Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Ryan Fields	SO	Washington University School of Medicine	Declared they had no conflicts of interest.
Sharlene Gill	MO	BC Cancer Agency	Declared they had no conflicts of interest.

Abbreviations: MO=medical 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 Strategy for Clinical Practice Guidelines, Systematic Reviews 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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. exp Evidence-Based Practice/
9. guideline.pt.
10. exp Practice Guideline/ or exp Guideline/
11. practice parameter$.tw.
12. exp Practice Guidelines as Topic/
13. practice guideline$.mp.
14. (guideline: or recommend: or consensus or standards).ti.
15. (guideline: or recommend: or consensus or standards).kw.
16. or/8-15
17. 7 and 16

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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. exp Evidence-Based Practice/
9. guideline.pt.
10. exp Practice Guideline/ or exp Guideline/
11. practice parameter$.tw.
12. practice guideline$.mp.
13. (guideline: or recommend: or consensus or standards).ti.
14. (guideline: or recommend: or consensus or standards).kw.
15. or/8-14
16. 7 and 15

Systematic Reviews

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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. exp Meta-Analysis as Topic/
9. meta-analysis.pt.
10. (systematic adj (review: or overview:)).mp.
11. (meta-analy: or metaanaly: or meta analy:).mp.
12. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
13. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
14. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or cancerlit or pubmed or pub-med or medline or med-line).ab.
15. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
16. or/8-15
17. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
18. (stud: adj1 select:).ab.
19. (17 or 18) and review.pt.
20. 16 or 19
21. 7 and 20
22. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
23. 21 not 22
24. limit 23 to yr="2000 -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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. exp meta analysis/
9. exp "meta analysis (topic)"/
10. exp "systematic review"/
11. exp "systematic review (topic)"/
12. (meta analy$ or metaanaly$ or meta-analy$).tw.
13. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
14. (systematic adj (review: or overview:)).tw.
15. exp "review"/ or review.pt.
16. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or cancerlit).ab.
17. (reference list$ or bibliograph$ or hand-search$ or relevant journal$ or manual search$).ab.

18. or/8-17
19. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
20. (study adj selection).ab.
21. (19 or 20) and review.pt.
22. 18 or 21
23. 7 and 22
24. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
25. 23 not 24
26. limit 25 to yr="2000 -Current"
27. limit 26 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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
9. animal/ not (exp human/ or humans/)
10. 8 or 9
11. 7 not 10
12. limit 11 to english language
13. limit 12 to yr="1990 -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$)).mp.
5. 3 and 4
6. hepatic arter$ infusion.mp.
7. 5 and 6
8. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
9. animal/ not (exp human/ or humans/)
10. 8 or 9
11. 7 not 10
12. limit 11 to english language
13. limit 12 to yr="1990 -Current"