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PRACTICE GUIDELINE

Liver resection for colorectal cancer metastases

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ABSTRACT

Questions

1. Should surgery be considered for colorectal cancer (CRC) patients who have liver metastases plus (a) pulmonary metastases, (b) portal nodal disease, or (c) other extrahepatic metastases (EHMS)?
2. What is the role of chemotherapy in the surgical management of CRC with liver metastases in (a) patients with resectable disease in the liver, or (b) patients with initially unresectable disease in the liver that is downsized with chemotherapy ("conversion")?
3. What is the role of liver resection when one or more CRC liver metastases have radiographic complete response (RCR) after chemotherapy?

Perspectives

Advances in chemotherapy have improved survival in CRC patients with liver metastases. The 5-year survival with chemotherapy alone is typically less than 1%, although two recent studies with FOLFOX or FOLFOXIRI (or both) reported rates of 5%–10%. However, liver resection is the treatment that is most effective in achieving long-term survival and offering the possibility of a cure in stage IV CRC patients with liver metastases. This guideline deals with the role of chemotherapy with surgery, and the role of surgery when there are liver metastases plus EHMS. Because only a proportion of patients with CRC metastatic disease are considered for liver resection, and because management of this patient population is complex, multidisciplinary management is required.

Methodology

Recommendations in the present guideline were formulated based on a prepublication version of a recent systematic review on this topic. The draft guideline underwent internal review by clinical and methodology experts, and external review by clinical practitioners. Feedback was incorporated into the final version of the guideline.

Practice Guideline

These recommendations apply to patients with liver metastases from CRC who have had or will have a complete (R0) resection of the primary cancer and who are being considered for resection of the liver, or liver plus specific and limited EHMS, with curative intent.

1(a). Patients with liver and lung metastases should be seen in consultation with a thoracic surgeon. Combined or staged metastasectomy is recommended when, taking into account anatomic and physiologic considerations, the assessment is that all pulmonary metastases can also be completely removed. Furthermore, liver resection may be indicated in patients who have had a prior lung resection, and vice versa.

1(b). Routine liver resection is not recommended in patients with portal nodal disease. This group includes patients with radiologically suspicious portal nodes or malignant portal nodes found preoperatively or intraoperatively. Liver plus nodal resection, together with perioperative systemic therapy, may be an option—after a full discussion with the patient—in cases with limited nodal involvement and with metastases that can be completely resected.

1(c). Routine liver resection is not recommended in patients with nonpulmonary EHMS. Liver plus extrahepatic resection, together with perioperative systemic therapy, may be an option—after a full discussion with the patient—for metastases that can be completely resected.

2(a). Perioperative chemotherapy, either before and after resection, or after resection, is recommended in patients with resectable

liver metastatic disease. This recommendation extends to patients with EHMS that can be completely resected (R0). Risks and potential benefits of perioperative chemotherapy should be discussed for patients with resectable liver metastases. The data on whether patients with previous oxaliplatin-based chemotherapy or a short interval from completion of adjuvant therapy for primary CRC might benefit from perioperative chemotherapy are limited.

2(b). Liver resection is recommended in patients with initially unresectable metastatic liver disease who have a sufficient downstaging response to conversion chemotherapy. If complete resection has been achieved, postoperative chemotherapy should be considered.

3. Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and when adequate functional liver can be left as a remnant. When a lesion with RCR is present in a portion of the liver that cannot be resected, surgery may still be a reasonable therapeutic strategy if all other visible disease can be resected. Postoperative chemotherapy might be considered in those patients. Close follow-up of the lesion with RCR is warranted to allow localized treatment or further resection for an *in situ* recurrence.

KEY WORDS

Colorectal cancer metastases, liver resection, hepatic resection, chemotherapy, complete response, downstaging

1. BACKGROUND

Advances in chemotherapeutic options have steadily improved survival for patients with stage IV colorectal cancer (CRC) and liver metastases. Recent clinical trials typically report median survival on the order of 20 months[1–7]. The 5-year survival with chemotherapy alone is historically less than 1%, although two recent clinical trials using front-line FOLFOX (folinic acid–5-fluorouracil–oxaliplatin) or FOLFOXIRI (folinic acid–5-fluorouricil–oxaliplatin–irinotecan), or both, reported 5-year survivals of 5%–10%[1,2].

Despite those advances, liver resection is the treatment that is most effective in achieving long-term survival and offering the possibility of cure in stage IV disease confined to the liver[4,5]. Patients with R0 resection of liver metastases have a 5-year survival rate of approximately 45% and a 10-year overall survival rate of 25%[4,5,8–12]. Because only a proportion of patients with CRC metastatic disease are considered for liver resection, and because management of this patient population is complex, multidisciplinary management is required.

1.1 Diagnosis and Assessment: Current Surgical Practice

1.1.1 Multidisciplinary Cancer Conference

Consistent with the multidisciplinary cancer conference (MCC) standards adopted by Cancer Care Ontario (CCO)[13,14] and the Hepatic, Pancreatic, and Biliary (HPB) Surgical Oncology Standards[15], patients should be fully informed, and cases should be reviewed at a MCC. The intent of the MCC is to ensure that all appropriate diagnostic tests and treatment options are generated and discussed prospectively with a multidisciplinary team having the knowledge and tools to provide a full array of surgical and interventional radiology procedures, systemic and radiation treatment, and supportive and palliative care. All patients with liver-only metastatic disease, or those with liver metastases and limited extrahepatic disease as discussed herein, should be considered for liver resection and referred to specialized centres. Treatment planning for patients with (potentially) resectable synchronous CRC and liver metastases was not within the scope of the literature review. For such patients, only limited level 1 evidence is available, and managment should be decided on a case-by-case basis in a MCC. Considerations for establishing a treatment plan, particularly with respect to the sequence of resection or possibly a combined resection, should include the extent of the primary lesion or lesions, associated symptoms, and the possibility of local control, balanced by the extent of liver metastases and the threat to achievement of a curative resection.

1.1.2 Resection of Liver-Only Metastases (Conclusions of Recent Consensus Groups or Reviews)

- Suspected metastases should be confirmed (usually with imaging and without biopsy) and staged by radiologic imaging.
- Overall health status, organ and liver function, and concomitant non-malignant disease must be assessed[16,17].
- If R0 with negative surgical margins (≥ 1mm) is possible and if sufficient liver parenchyma remains to maintain liver function, resection should be considered[16–19].
  - Two contiguous liver segments with intact vascular inflow and outflow and adequate biliary drainage are preserved20.
  - Remaining volume of liver (future liver remnant) is at least 20%–25%, or approximately 40% in cases of preoperative chemotherapy or other liver damage21–24.
- Downstaging or conversion chemotherapy [see question 2(b)], two-stage resection, portal vein embolization, and now associating liver partition with portal vein ligation for staged hepatectomy[25] are sometimes used in otherwise suitable candidates in whom the predicted liver remnant is too small.

- Radiofrequency ablation has been used for unresectable metastasis, sometimes in conjunction with the surgical removal of resectable metastases, and may have a role in the treatment of other selected patients[26–29].

1.2 Liver Resection in this Guideline

This guideline addresses liver resection in special cases of liver metastasis plus extrahepatic metastasis (EHM), or chemotherapy plus liver resection as described in the questions. It assumes that patients would meet the surgical criteria for resection of liver-only metastases.

2. METHODS

This practice guideline was developed by CCO's Surgical Oncology Program and the Program in Evidence-Based Care (PEBC) using the methods of the practice guidelines development cycle[30,31]. The PEBC was asked to prepare clinical care guidelines or recommendations using a draft version of a systematic review (now published[32]). The draft version was supplemented by additional information from the included studies considered important in the interpretation by the review authors[33]. The final version of the systematic review incorporated feedback obtained during the guideline development process.

This practice guideline is a convenient and up-to-date source of the best available evidence on the role of liver resection in CRC metastases, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The guideline is intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of CCO and the Ontario Ministry of Health and Long-Term Care.

2.1 Questions

1. Should surgery be considered for CRC patients who have liver metastases plus (a) pulmonary metastases, (b) portal nodal disease, or (c) other EHMs?
2. What is the role of chemotherapy in the surgical management of CRC with liver metastases in (a) patients with resectable disease in the liver, or (b) patients with initially unresectable disease in the liver that is downsized with chemotherapy ("conversion")?
3. What is the role of liver resection when one or more CRC liver metastases have radiologic complete response (RCR) after chemotherapy?

2.2 Target Population

The recommendations pertain to patients with liver metastases from CRC who have had or will have a complete (R0) resection of the primary cancer and who are being considered for resection of the liver, or liver plus EHMs, with curative intent.

2.3 Systematic Review

A systematic review on the role of liver resection for CRC was prepared by members of CCO's Surgical Oncology Program together with a team of Ontario surgeons and oncologists[32]. The review included a search of the MEDLINE and EMBASE databases from 1995 to January 2010, using the terms "colorectal neoplasm" or "colorectal cancer" as text or MESH and EMBASE subject headings. The results were combined with "liver neoplasm," "hepatectomy," "hepatic surgery," and "liver resection."

2.4 Outcomes of Interest

The primary outcomes were median survival, 3-year survival, and 5-year survival. The recurrence rate was also noted for question 1 (EHMs). Postoperative complications and chemotherapy-related hepatic injury were additional outcomes for question 2 (chemotherapy).

2.5 Development of Recommendations

This guideline was developed by the working group (authors), which included HPB surgeons and medical oncologists. During reading of the systematic review and preparation of the guideline, the group determined that additional information from the included studies might be important in their interpretation. Some of that information was incorporated into the final systematic review[32]; other details are given in the full evidence-based series[33]. The expert panel that was constituted for the development of the present guideline (see the Acknowledgments section) provided input on the guideline and recommendations drafted by the working group during a half-day meeting convened for that purpose. The participants represented the various sites in Ontario designated as HPB surgical centres (meeting the standards set by CCO) and included HPB surgeons and medical oncologists, together with radiologists, general surgeons, and a thoracic surgeon. The final version of the guideline incorporates suggestions from the internal and external review processes.

2.6 Internal and External Review

The draft report was reviewed by the PEBC Report Approval Panel, which consists of 2 members, including an oncologist with expertise in clinical and methodology issues. The PEBC Report Approval Panel reviewed the draft practice guideline and provided feedback, which was incorporated into the guideline before the revised draft report was sent for external review,

Links to the draft practice guideline and evidentiary base (Section 2 of the full guideline)[33], together with the Web address for the systematic review[32], were distributed for external review. The external review by clinical practitioners had two components. In the targeted peer review component, 5 reviewers considered experts on the topic were contacted. The 3 who agreed to participate answered a questionnaire evaluating the methods, recommendations, quality, and usefulness of the guideline, and also provided written comments. In the professional consultation component, links to the same material and a brief online survey were distributed to health care providers in the province of Ontario. Those providers included HPB community of practice members (excluding those on the expert panel), surgical oncology leads for each area of Ontario, thoracic community of practice members, medical oncologists with gastrointestinal interest or expertise, and general surgeons with gastrointestinal interest. Complete results from those two sources of feedback can be found in the full guideline report on the CCO Web site[33].

3. RESULTS AND DISCUSSION

3.1 Literature Search Results

The search resulted in 3610 non-duplicate articles, of which 83 were retained for inclusion in the review. Most of the included studies are retrospective or prospective case series. Three reports dealt with randomized controlled trials (RCTS) of chemotherapy. Details about the methodologic characteristics and clinical outcomes of the trials can be found in the systematic review[32] and the full guideline report on the CCO Web site[33].

3.2 Internal Review

The Report Approval Panel made several suggestions that were addressed and incorporated before the external review. Some of the major points are indicated here.

- It was suggested that the authors state in more explicit terms that the quality of evidence is poor, conclusions are thus not robust, and that recommendations are associated with limitations.
  - A preamble to the recommendations was added to address limitations of the evidence.
- The qualifying statement for question 2(a) (perioperative chemotherapy), related to the Sargent citation, appears to be overstated because the populations are very different.
  - This section was reworded to address the reviewer's comment.
- The report does not differentiate management, especially perioperative neoadjuvant or adjuvant chemotherapy, for patients who have or have not received adjuvant chemotherapy at the time of their initial diagnosis.
  - This question is outside the scope of the guideline, but some comments have been including in the qualifying statements for question 2(a).

3.3 External Review: Targeted Peer Review

In responses to the questionnaire, the guideline development methods, completeness, and overall quality were rated as high quality (at least 4 of 5), and ratings of 3.5 to 5 were given for the guideline recommendations. All respondents agreed or strongly agreed that they would use the guideline and recommend it to others. A summary of the main points follows.

- Reviewers indicated a desire for a discussion of the costs and risks of other options, of synchronous metastases and the timing of chemotherapy or resection, and of methods of staging.
  - These topics were outside the scope of the questions and systematic review. Some additional notes were placed in the Introduction.
- One reviewer disagreed with recommendation 2(a) and felt that the evidence was not sufficient to make such a strong recommendation in favour of chemotherapy based on current evidence (and even though it is widely practiced).
  - The authors felt that recommendation 2(a) is valid, despite the limited evidence. The recommendation should be read in conjunction with the qualifying statements, which were revised in response to the comment.

3.4 External Review: Professional Consultation

The feedback survey generated 23 responses. Of the 23 respondents, 22 considered the guideline to be of high quality (4 of 5 or 5 of 5) and agreed or strongly agreed (4 of 5 or 5 of 5) that they would use it in their professional decisions. All agreed or strongly agreed they would recommend it for use in practice. Written comments and responses of the working group are given in the full guideline[33].

- In recommendation 1(b), where does the recommendation for "+/– targeted therapy" come from?
  - Listing of chemotherapy agents, included targeted therapies, was deleted in recommendations 1(b) and 1(c) and was replaced with "perioperative systemic therapy." The qualifying statements for 2(a) were modified.
- I would remove the following wherever it appears: "A reasonable conclusion is that the evidence showing the benefit of adjuvant chemotherapy in stage 3 and high-risk stage 2 CRCS could be extrapolated to support a perioperative chemotherapy strategy in extrahepatic diseases." This is a huge extrapolation to a

completely different clinical scenario, and it's not necessary. The data, poor as they are, are enough to support the recommendations made.
  - The authors agreed that the original statement is valid, although the wording was adapted slightly as a result of the comment.
- Hepatic artery infusion (HAI) not mentioned and although not widely used does have some evidence in this situation. No discussion about what to do with perioperative chemotherapy (pre and post or all post) in patients already exposed to oxaliplatin earlier in a "true" adjuvant situation. This is a scenario increasing in incidence.
  - As indicated in Section 2, studies evaluating HAI as a technique were outside the scope of the literature review, although RCTs comparing various chemotherapy agents administered by HAI were included. A comment about treatment of patients previously receiving adjuvant therapy was added to the qualifying statements for question 2(a).
- Both perioperative chemotherapy and postoperative chemotherapy can be considered equally for the section on perioperative chemo for resectable liver disease.
  - Perioperative chemotherapy, defined as either before and after resection, or after resection, was recommended. Studies addressing the issue of the optimal timing of chemotherapy are limited.

4. CLINICAL PRACTICE GUIDELINE

The report *Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards,* a special report of CCO's PEBC[15] provides standards for the management of primary and secondary liver cancer in Ontario. Those standards include "a system of patient care that ensures multidisciplinary management, including Multidisciplinary Cancer Conferences (i.e., tumour boards), involving the appropriate health care professionals to ensure that patients receive the most appropriate treatment." Patients should be treated at a designated HPB centre.

As indicated in the key evidence and the qualifying statements following each recommendation, many of the studies available for the present review are noncomparative studies, with a lower quality of evidence than that from RCTs. There is potential for inherent bias, and differences in outcome between groups may be a result of differences in the characteristics of the groups rather than in the effect of the interventions. This field is rapidly evolving and the recommendations in the present guideline may be altered if results from additional RCTs become available.

4.1 Question 1

What is the role of liver resection in patients with EHMS?

4.1.1 Pulmonary Metastases

Recommendations: Patients with liver and lung metastases should be seen in consultation with a thoracic surgeon. Combined or staged metastasectomy is recommended when, taking into account anatomic and physiologic considerations, the assessment is that all pulmonary metastases can also be completely removed. Furthermore, liver resection may be indicated in patients who have had a prior lung resection, and vice versa.

Key Evidence: Evidence from non-controlled studies consistently suggests that a combined liver and lung metastasectomy leads to long-term survival (see Table 1 in the review by Quan *et al.*[32]). In studies with combined liver and lung resection, 3-year survival was 36%–59%, and 5-year survival was 9%–74%.

The relatively high survival of 74% reported by Shah *et al.*[34] was calculated from the date of the first metastasectomy instead of the second (usually pulmonary) metastasectomy as used in several other studies; however, the median overall survival was still 42.2 months after the last metastasectomy. In this study, patients with synchronous or metachronous presentation of liver and lung metastases had no statistically significant difference in overall survival. Survival may be higher than in other studies because of the use of aggressive surgical therapy plus pseudo-adjuvant chemotherapy after the liver resection (51% received 5-fluorouracil or irinotecan). Recurrence was treated with repeated liver metastasectomy in 7 patients (18%) and repeat lung resection in 12 patients (31%).

Qualifying Statements: The literature review tabulates the numbers of cases by order of resection (in some studies, the data are actually for the occurrence of metastases), but most of the original publications do not subdivide survival data according to the timing of resection. The order of surgery often reflects the order of occurrence and not a surgical choice. In cases of simultaneous hepatic and pulmonary metastases, several of the included studies state that hepatic metastasectomy was performed first. Shah *et al.*[34] indicate that this order was used to maintain pulmonary reserve and to rule out unexpected extrahepatic abdominal disease. Lung resection was performed 6 or more weeks later. Patients with completely resected lung or liver metastases who later developed metastases at the other site were not explicitly addressed in the review article; however, the evidence suggests that prior metastasectomy should not exclude the resection of new metastases.

4.1.2 Portal Node Metastases

Definition: Portal nodes are defined in the literature review as the lymph nodes found in the hepatoduodenal ligament. Jaeck *et al.*[35] divided the hepatic pedicle lymph nodes into area 1 (hepatoduodenal

ligament and retropancreatic portion) and area 2 (around the common hepatic artery and celiac axis).

Recommendations: Routine liver resection is not recommended in patients with portal nodal disease. This group includes patients with radiologically suspicious portal nodes or malignant portal nodes found preoperatively or intraoperatively. Liver plus nodal resection, together with perioperative systemic therapy, may be an option—after a full discussion with the patient—in cases with limited nodal involvement and metastases that can be completely resected. Chemotherapy is discussed in question 2 (see the qualifying statements).

Key Evidence: Patients with portal nodal disease have a worse prognosis than do those without EHMS (see Table 1 in Section 2 of the evidence-based series[33]). Although 5-year survival after liver resection was reported as 0% in some of the older studies, it is 12%–33% in the five most recent studies (see Table 1 in Section 2 of the evidence-based series[33]). The 3-year survival was 27%–56%.

Adam *et al.*[36] performed resections in patients responding to or stabilized with preoperative chemotherapy and found a 5-year survival of 25% with pedicular node involvement, and 0% with celiac or para-aortic involvement.

A later study by Jaeck's group[37] found that the involvement of either area 1 or area 2 nodes resulted in much better survival than if both areas were involved (3-year survival: 36% for one area vs. 18% for both areas; 5-year survival: 26% vs. 0%); adjuvant chemotherapy was an independent predictor of overall survival in multivariate analysis. These authors noted evolution in the treatment of colorectal liver metastases since their earlier study, including perioperative chemotherapy and aggressive surgical resection.

Qualifying Statements: Evidence is limited and based on prospective and retrospective case series of heterogeneous design. Studies include small numbers of highly selected patients, with surgery performed in a limited number of highly specialized centres. The location of nodes, microscopic or macroscopic involvement, type of surgery, extent of lymphadenectomy (complete, regional, or selected nodes), use and type of chemotherapy, and presence of other EHMS are not consistent across the studies. The 5-year follow-up is incomplete in several publications. Some studies conclude that portal nodal involvement should not be considered an absolute contraindication to the resection of colorectal liver metastases. Improvements in surgical techniques and preoperative treatment and the use of more effective chemotherapeutic agents all likely contributed to better survival in some of the recent studies.

Some members of the expert panel suggested resection only in patients with metastases that respond to chemotherapy. Adam *et al.*[36] used that criterion in their study, presumably based on their previous results,[38] but other publications concluded that the response to neoadjuvant chemotherapy did not correlate with overall survival[39]. No consensus was reached on this issue.

4.1.3 Metastases at Other Sites

Recommendations: Routine liver resection is not recommended in patients with nonpulmonary EHMS. Liver plus extrahepatic resection, together with perioperative systemic therapy, may be an option—after full discussion with the patient—for metastases that can be completely resected. Chemotherapy is discussed in question 2 (see the qualifying statements).

Key Evidence: In most reported studies, the 3-year survival after resection of liver plus EHMS is 20%–40% (see Table 3 of the review by Quan *et al.*[32]). The 5-year survival is 15%–32%. Overall, those rates are one third to one half those found in patients with resected liver metastases, but without EHM resection, although the data are not consistent across the various extrahepatic sites.

For peritoneal metastases, Elias *et al.*[40] reported 3-year and 5-year survival rates of 28% and 16%, and Carpizo *et al.*[41] reported survival rates of 41% and 30%.

Carpizo *et al.*[41] also found that ovarian metastases did not affect survival (5-year survival of 51% compared with 49% without EHM resection).

Two studies reported 0% survival with para-aortic lymph node metastases.

Several publications by Elias *et al.*[40,42,43] form the basis of the consensus of the European Colorectal Metastases Treatment Group[19], which is that "the presence of disease outside the liver should no longer be considered a strict contraindication for liver resection provided that the disease outside the liver is resectable."

The Consensus Conference of the American Hepato-Pancreato-Biliary Association[44] also concluded that "resection of intra-abdominal extrahepatic disease during hepatectomy for colorectal liver metastases should be performed provided a negative resection margin is achieved."

Qualifying Statements: An increasing number of institutions appear to be performing combined liver and EHM resection, although the evidence concerning outcomes is heterogeneous. The definitions for the site of disease, presentation of disease, and type of surgery performed vary among studies. Only four studies (see Table 3 in the systematic review[32]) reported separate data for multiple extrahepatic sites other than the hepatic lymph nodes.

4.2 Question 2

What is the role of chemotherapy in the surgical management of CRC liver metastases?

4.2.1 Resectable Disease

Does perioperative chemotherapy result in an improved outcome in patients having liver resection for CRC metastases?

Recommendations: Perioperative chemotherapy, either before and after resection, or after resection, is recommended in patients with resectable liver metastatic disease. This recommendation extends to patients with extrahepatic metastatic disease that can be completely resected (R0). Risks and potential benefits of perioperative chemotherapy should be discussed in patients with resectable liver metastases.

Key Evidence: The European Organisation for Research and Treatment of Cancer (EORTC) Intergroup trial 40983 reported by Nordlinger *et al.*[45] is a multicentre RCT comparing chemotherapy plus liver resection (6 cycles of FOLFOX4 before and 6 cycles after surgery) with surgery alone. Although 42% of the patients had previously received non-oxaliplatin adjuvant chemotherapy for the primary cancer, patients who had received oxaliplatin before trial start were excluded. The study was closed early (235 events accrued instead of the planned 278 events) because "events had not accumulated at the pace anticipated but the pressure from the medical community to have the trial results disclosed was very strong." They reported final progression-free survival (PFS) data for a protocol-unspecified interim time point, with overall survival not reported (still being monitored).

At interim analysis, based on intention to treat (all randomized patients), a 7.3% improvement in PFS was seen at 3 years in the surgery plus chemotherapy group, a trend that was not statistically significant (hazard ratio: 0.79; confidence interval: 0.62 to 1.02; $p = 0.058$). The median PFS was 18.7 months (compared with 11.7 months without chemotherapy). Reanalysis of the subsets of patients who were eligible ($n = 342$) or who had received resection ($n = 303$) indicated a significant increase in PFS for both subsets (hazard ratio: 0.77; confidence interval: 0.60 to 1.00; $p = 0.041$; and hazard ratio: 0.73; confidence interval: 0.55 to 0.97; $p = 0.025$ respectively).

Reversible postoperative complications occurred more often after chemotherapy than after surgery alone (25% vs. 16%, $p = 0.04$).

Perioperative chemotherapy reduced the relative risk of relapse by one quarter.

The only other randomized trials are reported by Mitry *et al.*[46] as a pooled analysis of two smaller studies [FFCD (Fédération Francophone de Cancérologie Digestive) trial 9002 and ENG (European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia) trial] of 5-fluorouracil postoperative chemotherapy that were both stopped early because of slow accrual. The FFCD trial excluded patients who had received chemotherapy in the year preceding liver surgery, and the ENG trial excluded patients with prior chemotherapy for metastatic disease or metastases diagnosed within 6 months of completion of adjuvant chemotherapy for the primary tumour. Trends in PFS and overall survival favoured the surgery-plus-chemotherapy group but did not reach statistical significance (median overall survival: 62.2 vs. 47.3 months; $p = 0.095$).

The 28-case series (see Table 4 in the review by Quan *et al.*[32]) were heterogeneous in regimens and outcomes. Preoperative chemotherapy-induced liver damage was identified in some of the studies.

Practice standards and guidelines support chemotherapy in metastasectomy patients.

An expert panel of the European Colorectal Metastases Treatment Group (including several participants in the EORTC 40983 trial) recommended that "the majority of patients with CRC liver metastases should be treated up front with chemotherapy, irrespective of the initial resectability status of their metastases"[47].

The Advanced Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines supports the use of perioperative chemotherapy[17].

The National Comprehensive Cancer Network practice guidelines for colon and rectal cancers also support chemotherapy plus resection for metastases[48,49].

Qualifying Statements: Although results from confirmatory trials are pending, the results from published evidence demonstrate consistent trends favouring perioperative chemotherapy to the extent that a widespread change in practice has occurred provincially and across other jurisdictions for the routine use of perioperative chemotherapy.

In stage III and high-risk stage II primary CRC, there is a well-known one-third relative risk reduction in recurrence with the use of adjuvant chemotherapy[50]. Clinicians have therefore often extrapolated that patients with resected metastatic disease are likely to benefit.

The most widely recommended perioperative chemotherapy based on that extrapolation and the recent EORTC 40983 trial results is an oxaliplatin-based combination. It is well-established that chemotherapy exposure may result in chemotherapy-induced liver damage or changes to the liver parenchyma. Differences in surgical outcomes resulting from different types of liver damage have been reported for irinotecan and oxaliplatin combination therapies, and have led to the preferential use of oxaliplatin-based combinations. In the appropriate settings, an irinotecan-based combination or fluoropyrimidine monotherapy may be a reasonable alternative.

Most studies recommend that the duration of preoperative chemotherapy be limited. Liver toxicity and RCR (see question 3) are more likely after prolonged exposure. Karoui *et al.*[51] found increased morbidity among patients receiving 6 or more cycles of chemotherapy. The Nordlinger *et al.* trial[45] limited preoperative chemotherapy to 6 cycles. Most of the preoperative chemotherapy studies for initially unresectable metastases [question 2(b)] performed repeat imaging during chemotherapy, with resection as soon as was technically feasible[52–54].

The randomized trials presented in this section's key evidence included patients who had previously received adjuvant chemotherapy, suggesting that prior adjuvant chemotherapy should not limit a patient's suitability for perioperative chemotherapy. The available data are insufficient to determine a minimum interval between completion of adjuvant therapy and initiation of perioperative chemotherapy for liver metastases. In the EORTC 40983 trial, no time limit before enrollment was imposed, but patients who had previously received oxaliplatin were excluded. In the pooled analysis by Mitry *et al.*[46], a 6-month minimum interval was required.

Although fewer data on resectable extrahepatic metastatic disease have been published, the recommendations with respect to perioperative chemotherapy extend to that patient population, based (as earlier mentioned) on an extrapolation of the available evidence in high-risk stage II and stage III CRC and perioperative results.

4.2.2 Initially Unresectable Disease

Should liver resection be performed in patients with initially unresectable metastatic liver disease after conversion chemotherapy?

Recommendations: Liver resection is recommended in patients with initially unresectable metastatic liver disease who have a sufficient downstaging response to conversion chemotherapy. If complete resection has been achieved, postoperative chemotherapy should be considered (see Resectable Disease).

Key Evidence: The data suggest that patients who are initially unresectable may benefit from chemotherapy to identify a subset of patients in whom successful conversion to resectability is achieved. In patients without EHMS, preoperative chemotherapy yielded a partial or complete clinical response in 25%–48% of patients, and led to complete resection in 15%–36% (see Table 5 in the review by Quan *et al.*[32]).

The foregoing finding is consistent with the consensus statement of the American Hepato-Pancreato-Biliary Association, which states that preoperative chemotherapy permits complete resection in 15%–30% of patients[44].

Survival rates after conversion chemotherapy plus liver resection were 52%–100% at 3 years (five studies) and 33%–43% at 5 years (three studies), similar to rates seen in patients considered resectable without chemotherapy in the same studies.

Qualifying Statements: This question deals primarily with CRC metastases to the liver only. Some of the patients in the reported studies had liver metastases plus EHMS, and the recommendations for question 1(c) would apply in such cases.

Multiple studies have suggested that some patients can be made resectable with chemotherapy, but no RCTs have been conducted, and the published studies are largely case series. Various definitions of "resectable" are used. There is no expectation that an RCT with a nonsurgical arm will be initiated in this patient population. Nonetheless, the potential for long-term survival suggested by the available data resulted in a strong consensus in the oncology community for widespread adoption of conversion chemotherapy with surgical intent.

Prolonged chemotherapy can result in liver toxicity [see question 2(a)], surgical complications, and RCR (see question 3). Most studies of preoperative chemotherapy for initially unresectable metastases used repeat imaging during chemotherapy, with resection as soon as was technically feasible[52–54]. In patients in whom resectability is achieved, it is common to offer further adjuvant chemotherapy, but no direct evidence is available on which to base a recommendation concerning either the utility of adjuvant chemotherapy or the total duration or number of cycles of chemotherapy.

4.3 Question 3

What is the role of liver resection when one or more liver metastases have RCR after chemotherapy?

Recommendations: Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and when adequate functional liver can be left as a remnant. When a lesion with RCR is present in a portion of the liver that cannot be resected, surgery may still be a reasonable therapeutic strategy if all other visible disease can be resected. Postoperative chemotherapy might be considered in such patients. Close follow-up of the lesion with RCR is warranted to allow for localized treatment or further resection for an *in situ* recurrence.

Key Evidence: Studies by Benoist *et al.*[55], Fiorentini *et al.*[56], and Tanaka *et al.*[57] (see Table 2 in Section 2 of the evidence-based series[33]) report the proportion of liver metastases with RCR located intraoperatively (37%, 49%, and 36% respectively), found during pathology examination of resected areas (80%, 63%, and 24%), and with recurrence (74%, 81%, and 41%). Complete response was 17%, 19%, and 51% of liver metastases.

Benoist *et al.*[55] and Elias *et al.*[42] respectively reported that 16% and 27% of patients experienced a true complete response.

Postoperative chemotherapy was given in all except one study (not mentioned by Fiorentini *et al.*[56]) and either to all patients or to those with missing liver metastases in an area that was not resected.

Four of the studies administered chemotherapy by HAI to either some or all patients. Elias *et al.*[58] found fewer recurrences with HAI than with systemic treatment.

Qualifying Statements: The foregoing studies provide evidence that a large proportion of liver metastases with RCR still contain viable tumour cells, but the studies were not designed to compare long-term survival between patients with RCR lesions that were resected and lesions that were left in place. The extrapolation of data from other studies suggests that resection should improve survival. Several articles on downstaging recommend limiting the duration of presurgical chemotherapy to minimize areas of liver metastases with RCR, which are then difficult to locate and resect[52–54]. Those studies used repeat imaging during chemotherapy, with resection as soon as was technically feasible.

5. REVIEW AND UPDATE

Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit the CCO Web site (http://www.cancercare.on.ca) for the full evidence-based series report[33] and subsequent updates.

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7. CONFLICT OF INTEREST DISCLOSURES

Authors disclosed potential conflicts of interest information. One of the authors (SG) received HPB fellowship support from Sanofi and from Roche. The other authors reported that they had no financial conflicts of interest.

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