Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 17-7 ARCHIVED

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

The Role of Liver Resection in Colorectal Cancer Metastases

Steven Gallinger, James J. Biagi, Glenn G. Fletcher, Cindy Nhan, Leyo Ruo, Robin S. McLeod, and the Expert Panel

Report Date: June 15, 2012

An assessment conducted in December 2020 ARCHIVED Evidence-based Series (EBS) 17-7. This means that the document will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 17-7 is comprised of 3 sections. You can access the full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2236

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Gallinger S, Biagi JJ, Fletcher GG, Nhan, C, Ruo L, McLeod RS; Expert G. The role of liver resection in colorectal cancer metastases. Toronto (ON): Cancer Care Ontario; 2012 June 15 [Archived 2020 Dec 9]. Program in Evidence-based Care Evidence-based Series No.: 17-7 ARCHIVED.

Journal Citation (Vancouver Style): Gallinger S, Biagi JJ, Fletcher GG, Nhan C, Ruo L, McLeod RS. Liver resection for colorectal cancer metastases. Curr Oncol. 2013;20(3):e255-65.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 17-7: Section 1

The Role of Liver Resection in Colorectal Cancer Metastases: Guideline Recommendations

Steven Gallinger, James J. Biagi, Glenn G. Fletcher, Cindy Nhan, Leyo Ruo, Robin S. McLeod, and the Expert Panel

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

Report Date: June 15, 2012

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 (EHM)?

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) following chemotherapy?

TARGET POPULATION

Patients with liver metastases from CRC who have had or will have an complete (R0) resection of the primary cancer and who are being considered for resection of the liver or liver plus extrahepatic metastasis with curative intent.

INTENDED USER

This guideline is targeted to surgeons and medical oncologists dealing with CRC patients with liver metastases.

BACKGROUND

In patients with CRC liver metastases, advances in chemotherapy have steadily improved survival. Recent clinical trials typically report median survival in the order of 20 months (1-7). Five-year survival with chemotherapy alone is historically less than 1%,

although two recent clinical trials using front-line FOLFOX and/or FOLFOXIRI report five-year survival of 5 to 10% (4,5). Despite these advances, liver resection is the most effective treatment that achieves long-term survival and that offers the possibility of cure in stage IV disease limited to the liver (6-7). Patients who have R0 resection of liver metastases have a five-year survival rate of approximately 45% and a 10-year overall survival rate of 25% (6-12).

The guideline recommendations are based on a recent systematic review of the published clinical evidence (13) and represent the consensus of the authors and members of the Expert Panel (listed in the Appendix, Section 1). The original publications of the primary studies were consulted when study details not reported in the systematic review were required. As indicated in the Key Evidence and Qualifying Statements following each recommendation, many of the studies available for this review are non-comparative studies, with a lower quality of evidence than from randomized controlled trials (RCTs). There is a greater potential for inherent bias, and the differences in outcome between groups may be due to differences in the characteristics of the groups rather than the effect of the interventions. This is a rapidly evolving field and the recommendations in this guideline may be altered if the results from additional RCTs become available.

Diagnosis and Assessment: Current Surgical Practice

Multidisciplinary Cancer Conference

Consistent with the multidisciplinary cancer conference (MCC) standards adopted by Cancer Care Ontario (CCO) (14,15) and the hepatic, pancreatic, and biliary (HPB) surgical oncology standards (16), patients should be fully informed and reviewed at an 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 interventions, systemic and radiation treatments, 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. This is an area with only limited Level 1 evidence, and patients should be dealt with on a case-by-case basis in MCC. Considerations for establishing a treatment plan, particularly with respect to the sequence of resections or possibly a combined resection, should include the extent of the primary lesion(s), associated symptoms and possibility of local control, balanced by the extent of liver metastases and the threat to achieving a curative resection.

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

- Suspected metastases should be confirmed and staged by radiological imaging.
- Overall health status, organ/liver function, and concomitant non-malignant disease must be assessed (17,18).
- If R0 with negative surgical margins (≥1mm) is possible and sufficient liver parenchyma remains to maintain liver function, resection should be considered (17-20).
    - Two contiguous liver segments with intact vascular inflow and outflow and adequate biliary drainage are preserved (21)
    - Remaining volume of liver (future liver remnant) is at least 20% to 25%, or 40% in cases of preoperative chemotherapy or other liver damage (22-26).
- Downstaging/conversion chemotherapy (see Question 2b), two-stage resection, and portal vein embolization (PVE) are sometimes used in otherwise suitable candidates where the predicted liver remnant is too small.

- Radiofrequency ablation (RFA) 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 (27-30).

Liver Resection in this Guideline

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

RECOMMENDATIONS AND KEY EVIDENCE

The CCO/PEBC special report "Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards" (16) provides standards for the management of primary and secondary liver cancer in Ontario. These requirements 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 that has appropriate physical resources (diagnostic equipment, operating rooms, intensive care unit [ICU]), staffing (surgeons with advanced training in HPB surgery, nurses, radiologists, medical and radiation oncologists), and a high volume of HPB surgeries (a minimum of 50 index HPB cases per year).

1. What is the role of liver resection in patients with extrahepatic metastases (EHM)?

1a) Pulmonary Metastases
Recommendation

Patients with liver and lung metastases should be seen in consultation by 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 previous 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 (13)). In studies with combined liver and lung resection, three year survival was 36% to 59%, and five year survival was 9% to 74%.

- The relatively high survival of 74% reported by Shah et al (31) was calculated from the date of the first metastasectomy instead of the second (usually pulmonary) metastectomy 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. Shah et al (31) reported the use of aggressive surgical therapy plus pseudoadjuvant chemotherapy (after potentially curative metastasectomy) following the liver resection (51% received 5-fluorouracil [5FU] or irinotecan). Recurrence was treated with repeated liver metastasectomy in seven patients (18%) and repeat lung resections in 12 patients (31%).

Qualifying Statements

While the literature review tabulates the numbers of cases by the order of resection (in some studies, the data are actually for the occurrence of metastases), most of the original publications do not subdivide survival data according to the timing of resection. The order of surgery is often a reflection of 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 metastectomy was performed first. Shah et al (31) indicate that this was to maintain pulmonary reserve and rule out unexpected extrahepatic abdominal disease; lung resection was performed six weeks later. Patients with either 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 metastectomy should not exclude the resection of new metastases.

1b) Portal Node Metastases

Definition

Portal nodes are defined in the literature review as those lymph nodes that are found in the hepatoduodenal ligament. Jaeck et al (32) divide the hepatic pedicle lymph nodes into Area 1 (hepatoduodenal ligament and retropancreatic portion) and Area 2 (around the common hepatic artery and celiac axis).

Recommendation

***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, along with perioperative systemic therapy, may be an option, after a full discussion with patients, in cases with limited nodal involvement and metastases that can be completely resected. Chemotherapy is discussed in Question 2 (see qualifying statements).**

Key Evidence

- Patients with portal nodal disease have a worse prognosis than do those without EHM (see Table 1 in Section 2).
- While five-year survival after liver resection was reported as 0% in some of the older studies, it is 12% to 33% in the five most recent studies (see Table 1 in Section 2). The three-year survival was 27% to 56%.
- Adam et al (33) performed resections in patients responding to or stabilized with preoperative chemotherapy and found a five-year survival of 25% with pedicular node involvement, and 0% with celiac or para-aortic involvement.
- A later study by Jaeck et al (34) found that the involvement of either Area 1 or Area 2 nodes resulted in much better survival than if both areas were involved (three-year survival 36% for one area versus 18% for both areas; five year survival 26% versus 0%); adjuvant chemotherapy was an independent predictor of overall survival in multivariate analysis. They noted the evolution in treatment of colorectal liver metastases since their previous 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/selected nodes), use and type of chemotherapy, and presence of other EHM are not consistent across the studies. Five-year follow-up is incomplete in several publications. Some studies conclude that portal nodal involvement should not be considered an absolute contraindication for the resection of colorectal liver metastases. The improvement in surgical techniques, preoperative treatment, and use of more effective chemotherapeutic agents all likely contributed to better survival in some of the recent studies.

Some members of the Expert Panel (Appendix 1) suggested resection only in patients with metastases that respond to chemotherapy. While Adam et al (33) used this criterion in their study, presumably based on their previous results (35), other publications concluded the response to neoadjuvant chemotherapy did not correlate with overall survival (36). No consensus was reached on this issue.

1c) Metastases at Other Sites
Recommendation

***Routine* liver resection is not recommended in patients with non-pulmonary EHM. Liver plus extrahepatic resection along with perioperative systemic therapy may be an option, after full discussion with patients, for metastases that can be completely resected. Chemotherapy is discussed in Question 2 (see qualifying statements).**

Key Evidence

- Three-year survival following resection of liver plus EHM is 20% to 40% in most reported studies (see Table 3 of the review by Quan et al (13)). Five-year survival is 15% to 32%. Overall these rates are one third to one half of those found in patients with resected liver metastases but without EHM, though data are not consistent across the various extrahepatic sites.

- For peritoneal metastases, Elias et al (37) reported three-year and five-year survival rates of 28% and 16%, while Carpizo et al (38) reported survival rates of 41% and 30%.

- Carpizo et al (38) also found that ovarian metastases did not affect survival (five-year survival of 51% compared to 49% without EHM).

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

- Several publications by Elias et al (37,39,40) form the basis of the consensus of the European Colorectal Metastases Treatment Group (20), 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 (41) 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

There appears to be an increasing number of institutions performing combined liver resection and resection of EHM, although the evidence on outcomes is heterogeneous. The

definitions for the site of disease, presentation of disease, and type of surgery performed differ among studies. Only four studies (see Table 3 in the review (13)) reported separate data for multiple extrahepatic sites other than the hepatic lymph nodes.

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

2a) Resectable disease: Does perioperative chemotherapy result in an improved outcome in patients having liver resection for CRC metastases?

Recommendation

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 Organization for Research and Treatment of Cancer (EORTC) Intergroup trial 40983 reported by Nordlinger et al (42) is a multicentre RCT comparing chemotherapy plus liver resection (six cycles of FOLFOX4 before and six cycles after surgery) to surgery alone. While 42% of the patients had previously received non-oxaliplatin adjuvant chemotherapy for the primary cancer, patients who had received oxiplatin prior to the trial start were excluded. The study was closed early (235 events accrued instead of the planned 278 events) as "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), there was a 7.3% improvement in PFS at three years in the surgery plus chemotherapy group, a trend that was not statistically significant (hazard ratio [HR], 0.79; confidence interval [CI], 0.62 to 1.02; p=0.058). The median PFS was 18.7 months versus 11.7 months without chemotherapy. Reanalysis of the subset of patients who were eligible (n=342) or received resection (n=303) indicated a significant increase in PFS (HR, 0·77; CI, 0·60–1·00; p=0·041), and (HR, 0.73; CI, 0.55 to 0.97; p=0.025), respectively.
  - Reversible postoperative complications occurred more often after chemotherapy than with surgery alone (25% versus 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 (43) as a pooled analysis of two smaller studies (FFCD Trial 9002 and ENG Trial) of 5FU postoperative chemotherapy that were both stopped early due to slow accrual. The FFCD trial excluded patients who had received chemotherapy in the year preceding liver surgery, while the ENG trial excluded patients with prior chemotherapy for metastatic disease or metastases diagnosed within six months of completion of adjuvant chemotherapy for the primary tumour. There were trends in PFS and overall survival favouring the surgery plus chemotherapy group (median overall survival, 62.2 versus 47.3 months; p=0.095) that did not reach statistical significance.

- The 28 case series (see Table 4 in the review by Quan et al (13)) were heterogeneous in regimens and outcomes. Preoperative chemotherapy-induced liver damage (CILD) was

identified in some of the studies.

- Practice standards and guidelines support chemotherapy in metastectomy patients.
  - An expert panel of the European Colorectal Metastases Treatment Group (including several participants of the EORTC 40983 trial) recommends 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"(44).
  - The Advanced Colorectal Cancer: ESMO Clinical Practice Guidelines supports the use of perioperative chemotherapy (18).
  - NCCN practice guidelines for colon and rectal cancers also support chemotherapy plus resection for metastases (45,46).

Qualifying Statements

While results from confirmatory trials are awaited, the results from current evidence demonstrate consistent trends that favour perioperative chemotherapy, to the extent that there has been a widespread change in practice provincially and across other jurisdictions for the routine use of perioperative chemotherapy.

In stage 3 and high-risk stage 2 primary CRC, there is a well-known one-third relative risk reduction in recurrence with the use of adjuvant chemotherapy (47). Clinicians have therefore often extrapolated that patients with resected metastatic disease are likely to benefit.

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

Most studies recommend that the duration of preoperative chemotherapy be limited. Liver toxicity and radiographic complete response (see Question 3) are more likely after prolonged exposure. Karoui et al (48) found increased morbidity among patients with six or more cycles of chemotherapy, and the Nordlinger et al trial (42) limited preoperative chemotherapy to six cycles. Most of the preoperative chemotherapy studies for initially unresectable metastases (Question 2b) performed repeat imaging during chemotherapy with resection as soon as was technically feasible (49-51).

The randomized trials presented in the Key Evidence section above included patients who previously received adjuvant chemotherapy, suggesting that prior adjuvant chemotherapy should not limit a patient's suitability for perioperative chemotherapy. The available data do not provide sufficient evidence to determine what time frame is sufficient after completion of adjuvant chemotherapy before perioperative chemotherapy for liver metastases is instituted. In the EORTC 40983 trial, there was no time limit prior to enrolment, but patients who received previous oxaliplatin were excluded; in the pooled analysis by Mitry, a six-month minimum interval was required.

Although there are fewer published data on resectable extrahepatic metastatic disease, the recommendations of perioperative chemotherapy extend to this patient population, based (as above), on extrapolation of the available evidence in high-risk stage 2 and stage 3 CRC and perioperative results.

2b) Initially unresectable disease: Should liver resection be performed in patients with initially unresectable metastatic liver disease following conversion chemotherapy?

Recommendation

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

Key Evidence

- The data suggest that patients who are initially unresectable may benefit from receiving chemotherapy in order to identify a subset of patients in whom successful conversion to resectability is achieved. In patients without EHM, preoperative chemotherapy gave a partial or complete clinical response in 25% to 48% of patients, and led to complete resection in 15% to 36% (see Table 5 in the review by Quan et al (13)).

- This finding is consistent with the consensus statement of the American Hepato-Pancreato-Biliary Association, which states that preoperative chemotherapy permits complete resection in 15% to 30% of patients (41).

- Survival rates after conversion chemotherapy plus liver resection was 52% to 100% at three years (five studies) and 33% to 43% at five years (three studies), similar to rates in patients considered resectable without chemotherapy in these studies.

Qualifying Statements

This question dealt primarily with CRC metastases only to the liver. Some of the patients in the reported studies had liver plus EHM, and the recommendations for Question1c would apply in these cases.

While multiple studies have suggested that some patients can be made resectable via chemotherapy, there are no RCTs, and these studies are largely case series. Different definitions of resectable were used. There is no expectation that an RCT with a non-surgical arm will be initiated in this patient population. Nonetheless, the data point to the potential for long term survival that has resulted in strong consensus in the oncology community for the widespread adoption of conversion chemotherapy with surgical intent.

Prolonged chemotherapy can result in liver toxicity (see Question 2a), surgical complications, and RCR (see Question 3). Most of the studies of preoperative chemotherapy for initially unresectable metastases used repeat imaging during chemotherapy with resection as soon as was technically feasible (49-51). In patients where resectability is achieved, while it is common to offer further adjuvant chemotherapy, there is no direct evidence that would allow us to make a recommendation on either the utility of adjuvant chemotherapy, or total duration or number of cycles, of chemotherapy.

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

Recommendation

Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and 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 these patients. Close follow-up of the lesion with RCR is warranted to allow localized treatment or further resection for an in-situ recurrence.

Key Evidence

- Studies by Benoist et al (52), Fiorentini et al (53), and Tanaka et al (54) (see Table 2 in Section 2) report the proportion of liver metastases with RCR located intraoperatively (37%, 49%, and 36%, respectively), found by pathologic 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 (52) and Elias et al (39) reported that 16% and 27%, respectively, of *patients* had a true complete response.

- Postoperative chemotherapy was given in all except one study (not mentioned by Fiorentini et al (53)) 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 hepatic arterial infusion (HAI) to either some or all patients. Elias et al (55) found lower recurrence with HAI than with systemic treatment.

Qualifying Statements

These 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 those 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 in order to minimize areas of liver metastases with RCR, which are then difficult to locate and resect (49-51). These studies used repeat imaging during chemotherapy with resection as soon as was technically feasible.

RELATED PEBC GUIDELINES

- Marcaccio M, Langer B, Rumble B, Hunter A; Expert Panel on HPB Surgical Oncology. Hepatic, pancreatic, and biliary tract (HPB) surgical oncology standards [Internet]. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 14. Program in Evidence-based Care (PEBC) Special Report Evidence-based Series No.: 17-2. Available from: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10418
- Jonker D, Spithoff K, Maroun J; Gastrointestinal Cancer Disease Site Group. Adjuvant systemic chemotherapy for stage II and III colon cancer following complete resection [Internet]. Toronto (ON): Cancer Care Ontario (CC0);.2008 Apr. Program in Evidence-Based Care (PEBC) Evidence-Based Series No.: 2-29. Available from: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10207
- Wong R, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, et al. Preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer [Internet]. Toronto (ON): Cancer Care Ontario (CC0); 2008 Jul. Program in Evidence-Based Care (PEBC) Evidence-Based Series No.: 2-4. Available from: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10207
- Smith AJ, Driman DK, Spithoff K, McLeod R, Hunter A, Rumble RB, et al. Optimization of surgical and pathological quality performance in radical surgery for colon and rectal

cancer: margins and lymph nodes [Internet]. Toronto (ON): Cancer Care Ontario (CCO); 2008 Apr. Program in Evidence-Based Care (PEBC) Evidence-Based Series No.17-4. Available from: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10418

Updating

This document will be reviewed in three years to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chien CRC, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408-17.
2. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.
3. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrine G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25(13):1670-6.
4. Sanoff HK, Sargent DJ, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol. 2008;26(35):5721-7.
5. Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, Baldi G, Salvatore L, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst. 2011;103(1):21-30.
6. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: Impact of surgical resection on the natural history. Br J Surg. 1990; 77(11):1241-6.
7. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet. 1994;343(8910):1405-10.
8. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Cancer. 1996;77(7):1254-62.
9. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759-66.
10. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818-25.
11. Jonas S, Thelen A, Benckert C, Spinelli A, Sammain S, Neumann U, et al. Extended resections of liver metastases from colorectal cancer. World J Surg. 2007;31(3):511-21.
12. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg. 2007;205(5):676-83.
13. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery 2012; 151(6):860–70. Epub 2012 Feb 7. doi: 10.1016/j.surg.2011.12.018.
14. Wright FC, De Vito C, Langer B, Hunter A; Expert Panel on Multidisciplinary Cancer Conference Standards. Multidisciplinary cancer conference standards [Internet]. Toronto (ON): Cancer Care Ontario; 2006 Jun 1. Program in Evidence-based Care Evidence-based Series No.: 15-7. Available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=1431
15. Wright FC, De Vito C, Langer B, Hunter A; Expert Panel on Multidisciplinary Cancer Conference Standards. Multidisciplinary cancer conferences: A systematic review and development of practice standards. Eur J Cancer. 2007;43(6):1002-10.

16. Marcaccio M, Langer B, Rumble B, Hunter A; Expert Panel on HPB Surgical Oncology. Hepatic, pancreatic, and biliary tract (HPB) surgical oncology standards. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 14. Program in Evidence-based Care Special Report Evidence-based Series No.: 17-2. Available from: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10418
17. Penna C, Nordlinger B. Colorectal metastases (liver and lung). Surg Clin North Am. 2002;82(5):1075-90.
18. Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Ann Oncol. 2010;21(Suppl 5):v93-v97.
19. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005;241(5):715-24.
20. Van Cutsem E, Nordlinger B, Adam R, Kohne CH, Pozzo C, Poston G, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer. 2006;42(14):2212-21.
21. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1261-8.
22. Azoulay D, Castaing D, Smail A, Adam R, Caillez V, Laurent A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg. 2000;231(4):480-6.
23. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery. 2000;127:512-9.
24. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH, et al. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg. 2004; 239(5):722-32.
25. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg. 2002;137(6):675-81.
26. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg. 2003;7(3):325-330.
27. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol. 2009;19(5):1206-13.
28. McKay A, Fradette K, Lipschitz J. Long-term outcomes following hepatic resection and radiofrequency ablation of colorectal liver metastases. HPB Surgery [Internet]. 2009. doi:10.1155/2009/346863. Available from: http://www.hindawi.com/journals/hpb/2009/346863.html
29. Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009;45(10):1748-56.
30. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd 3rd GD, Dorfman GS, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493-508.
31. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg. 2006;202(3):468-475.
32. Jaeck D, Nakano H, Bachellier P, Inoue K, Weber JC, Oussoultzoglou E, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. Ann Surg Oncol. 2002;9(5):430-8.

33. Adam R, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol. 2008;26(22):3672-80.
34. Oussoultzoglou E, Romain B, Panaro F, Rosso E, Pessaux P, Bachellier P, et al. Long-term survival after liver resection for colorectal liver metastases in patients with hepatic pedicle lymph nodes involvement in the era of new chemotherapy regimens. Ann Surg. 2009;249(6):879-86.
35. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004; 240(4):644-58
36. Gallagher DJ, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, et al. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Ann Surg Oncol. 2009;16(7):1844-51.
37. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg. 2003;90(5):567–74.
38. Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gonen M, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol. 2009;16(8):2138-46.
39. Elias D, Sideris L, Pocard M, Ouellet JF, Boige V, Lasser P, et al. Results of R0 resection for colorectal liver metastases associated with extrahepatic disease. Ann Surg Oncol. 2004;11(3):274–80.
40. Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol. 2005;12(11):900–9.
41. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1271-80.
42. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Peri-operative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007-16.
43. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26(30):4906-11.
44. Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol. 2009;20(6):985-92.
45. NCCN Clinical Practice Guidelines in Oncology. Colon cancer [Internet]. Version 2.2011 Fort Washington (PA): National Comprehensive Cancer Network (NCCN); 2011 [cited 2011 Jan 25]. Available from: http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf.
46. NCCN Clinical Practice Guidelines in Oncology. Rectal cancer [Internet]. Version 2.2011. Fort Washington (PA): National Comprehensive Cancer Network (NCCN); 2011 [cited 2011 Jan 25] Available from: http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf
47. Sargent D, Sobrero A, Grothey A, O'Connell MJ, Buyse M, Andre T, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009;27(6):872-7.

48. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006;243(1):1-7.
49. Nuzzo G, Giuliante F, Ardito F, Vellone M, Pozzo C, Cassano A, et al. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. J Gastrointest Surg. 2007;11:318-24.
50. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Ann Surg. 2009;249(3):420-5.
51. Skof E, Rebersek M, Hlebanja Z, Ocvirk J. Capecitabine plus irinotecan (XELIRI regimen) compared to 5-FU/LV plus irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. BMC Cancer [Internet]. 2009;9(120). Available from: http://www.biomedcentral.com/1471-2407/9/120
52. Benoist S, Brouquet A, Penna C, Julie C, El Hajjam M, Chagnon S, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006;24:3939-45.
53. Fiorentini G, Del Conte A, De Simone M, Guadagni S, Mambrini A, D'Alessandro M, et al. Complete response of colorectal liver metastases after intra-arterial chemotherapy. Tumori. 2008;94(4):489-92.
54. Tanaka K, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. Ann Surg. 2009;250(6):935-942.
55. Elias D, Goere D, Boige V, Kohneh-Sharhi N, Malka D, Tomasic G, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. Ann Surg Oncol. 2007;14(11):3188-3194.

Section 1 Appendix. Working Group and Expert Panel Members

Working Group

- **Dr. Steven Gallinger*** (chair), Surgeon, University Health Network, Toronto, Ontario
- **Dr. James J. Biagi***, Medical Oncologist, Cancer Centre of South-eastern Ontario, Queen's University, Kingston, Ontario
- **Glenn G. Fletcher***, Research Coordinator, PEBC, Cancer Care Ontario/McMaster University, Hamilton, Ontario
- **Amber Hunter**, Manager, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario
- **Cindy Nhan***, Project Coordinator, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario
- **Dr. Leyo Ruo***, Surgeon, McMaster University Medical Centre, Hamilton, Ontario
- **Dr. Robin S. McLeod***, Surgeon, Mount Sinai Hospital *and* Lead, Quality Improvement & Knowledge Transfer, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario

Expert Panel

- **Dr. Rebecca A. Auer***, Surgeon, The Ottawa Hospital, Ottawa, Ontario
- **Dr. Fady Balaa,** General Surgeon, The Ottawa Hospital, Ottawa, Ontario
- **Dr. Pablo Cano**, Medical Oncologist, Northeastern Ontario Regional Cancer Centre, Sudbury, Ontario
- **Dr. Eric Chen,** Medical Oncologist, Princess Margaret Hospital/UHN, Toronto, Ontario
- **Dr. Marc DePerrot,** Thoracic Surgeon, University Health Network, Toronto, Ontario
- **Dr. Ehsan Haider,** Radiologist, Hamilton Health Sciences/McMaster University, Hamilton, Ontario
- **Dr. Richard Hart,** HPB Surgeon, St Joseph's Hospital, Toronto, Ontario
- **Dr. Mohamed Husien**, HPB Surgeon, Grand River Hospital, Waterloo, Ontario
- **Dr. Diederick Jalink,** HPB Surgeon, Kingston General Hospital/Queen's University, Kingston, Ontario
- **Dr. John Kachura,** Radiologist, University Health Network, Toronto, Ontario
- **Dr Leonard Kaizer,** Medical Oncologist, Credit Valley Hospital, Mississauga, Ontario
- **Dr. Calvin H.L. Law***,HPB Surgeon, Sunnybrook Health Sciences Centre, Toronto, Ontario
- **Dr. Callista Philipps**, Medical Oncologist, Joseph Brant Hospital, Burlington, Ontario *and* McMaster University, Hamilton, Ontario
- **Dr. Doug Quan***, HPB Surgeon, London Health Science Centre, London, Ontario
- **Dr Jeffrey Rothenstein,** Medical Oncologist, Durham Regional Cancer Center, Lakeridge Health, Oshawa, Ontario
- **Dr. Stephen Welch,** Medical Oncologist, London Health Sciences Centre, London, Ontario
- **Dr. Joe Wen,** HPB Surgeon, Credit Valley Hospital/ Trillium Health Centre, Mississauga, Ontario

* Author of the review article on which this guideline is based.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 17-7: Section 2

The Role of Liver Resection in Colorectal Cancer Metastases: Evidentiary Base

Steven Gallinger, James J. Biagi, Glenn G. Fletcher, Cindy Nhan, Leyo Ruo, Robin S. McLeod, and the Expert Panel

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

Report Date: June 15, 2012

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 (EHM)?

2. What is the role of chemotherapy in the surgical management of CRC with liver metastases in (a) patients with resectable disease, and (b) patients with initially unresectable disease that becomes downsized with chemotherapy (conversion)?

3. What is the role of liver resection when one or more liver metastases have radiographic complete response (RCR) following chemotherapy?

INTRODUCTION

A systematic review addressing the above questions was prepared by members of the Surgical Oncology Program at Cancer Care Ontario (CCO) together with a team of Ontario surgeons and oncologists (1).

The Program in Evidence-Base Care (PEBC) was asked to prepare Clinical Care Guidelines/Recommendations using a draft version of this review as the evidence base. The review was rated as 5/11 points using the AMSTAR tool (see Appendix 1) (2). Two of the questions were judged not applicable, making the effective rating 5/9. The description below applies to the systematic review and only a brief summary of the results is given. Additional evaluation of the original publications by the Working Group is reported at the end of this section.

QUAN ET AL (1) REVIEW

METHODS

Literature Search Strategy

MEDLINE and EMBASE databases were searched in January 2010, using the terms 'colorectal neoplasm' or 'colorectal cancer' as text or MeSH/EMBASE subject headings. These results were combined with 'liver neoplasm,' 'hepatectomy,' 'hepatic surgery,' and 'liver resection.' In addition, the reviewer (CN) consulted with content experts and hand-searched the reference lists of the included articles and review articles found in the search. The results were restricted to full English language reports of human studies published from 1995 to the first week of January 2010.

Study Selection Criteria

Inclusion Criteria

- Randomized controlled trials (RCTs) with > 50 patients
- Prospective or retrospective case series with the following:
  a) Question 1c, 2a, 2b: >50 patients*
  b) Question 1a, 1b: > 25 patients*
  c) Question 3: No sample size limit

* Total number of patients in the study; the number of patients with the disease of interest was often less.

Exclusion Criteria

- Editorials, letters, comments; narrative reviews, unless there was an explicitly defined systematic literature search.
- Studies assessing radiofrequency ablation, portal vein embolization, hepatic arterial infusion for administering chemotherapy, photodynamic therapy, or repeat liver resections. Studies using (but not focusing on or assessing) these techniques in conjunction with liver resection were not excluded.
- Studies reporting treatment of primary CRC only.
- Studies assessing liver transplantation.
- Studies reporting only markers and enzymes outcomes or quality of life outcomes.

Outcomes of Interest

The primary outcomes were median survival, three-year survival, and five-year survival. The recurrence rate was also noted for Question 1 (EHM). Postoperative complications and chemotherapy-related hepatic injury were additional outcomes for Question 2 (chemotherapy).

RESULTS

Literature Search Results

The search resulted in 3610 non-duplicate articles that were initially screened using the citation and abstract by one of the authors (CN). Six hundred fifty-nine (659) full publications were obtained and screened by two authors (CN and RM), and 83 of these articles were retained for inclusion in the review. One reviewer (CN) extracted the data, and in cases of uncertainty the results were reviewed by a second reviewer (RM).

Studies Included

Most of the studies included are retrospective or prospective case series. In addition, there are three reports of randomized control trials (RCTs) of chemotherapy.

Compilation of Study Results

The data from the relevant publications were extracted and compiled in a separate table for each question.

Summary of Studies

1a) Liver plus Pulmonary Resection

Fourteen studies with liver and lung resection were included in the review. There was a median of 30 patients (n=15-131). The two largest studies (> 50 patients) reported a five-year survival of about 30%.

1b) Portal Nodal Disease

Portal nodes are defined in the literature review as those lymph nodes found in the hepatoduodenal ligament. Of 16 articles listed in the review, six were not included in the analysis as they gave only a general description of nodal location (regional, extrahepatic, or abdominal). All the studies included only small numbers of patients (n=7-35) with lymph node involvement. The five-year survival was 0% in two studies, and from 5% to 33% in six other studies, compared to 26% to 53% in patients without lymph node involvement.

1c) Liver plus Other Metastases

Of the fourteen studies included in the review, six did not specify the extrahepatic sites or give a breakdown of survival by site. The five-year survival was from 0% to 51%. Carpizo et al (3) reported the five year survival by site as 23% locally invasive (histological invasion of the diaphragm, portal vein, vena cava, or right adrenal/kidney), 30% peritoneum, 51% ovary, and 28% multiple sites, compared to 49% in patients without EHM.

2a) Chemotherapy in Resectable Liver Metastases

The review included 28 retrospective or prospective case series , one multinational RCT of perioperative chemotherapy plus surgery versus surgery (4) (European Organization for Research and Treatment of Cancer [EORTC] Intergroup trial 40983), and one study presenting a pooled analysis of two RCTs of postoperative chemotherapy (5). The RCTs reported improvements in progression free survival (PFS), though not quite reaching statistical significance. The non-randomized trials used a variety of chemotherapy regimes, cycles, and timing with respect to surgery.

2b) Conversion Chemotherapy in Initially Unresectable Liver Metastases

The review consisted of 10 studies. An average of 14% of patients underwent liver resection. In five studies the three-year survival was from 52% to 100%, and was similar to survival in patients with liver resection who were considered resectable without chemotherapy. Two studies reported the five-year survival, 42% for one and 33% for the other.

3. Radiographic Complete Response Following Chemotherapy

Five studies were included that dealt specifically with liver resection when there is an RCR to chemotherapy (lesions no longer visible on cross-sectional imaging). They reported percentages for the proportion of "missing" liver metastases located intraoperatively (37%, 49%, and 36%), found by pathologic examination of resected areas (80%, 63%, and 24%), or with recurrence (74%, 81%, and 41%). Complete response was therefore 17%, 19%, and 51% of lesions or 16%, 27%, and 62% of patients.

CONCLUSIONS

The overall conclusion was that "a multidisciplinary approach, including surgeons, medical oncologists, and interventional radiologists is critical to improve outcomes." Specific conclusions were given for each question.

- In a highly select patient group with pulmonary metastatic disease, liver and lung resection may be performed with reasonable outcomes if all pulmonary metastases and liver metastases can be completely removed.
- Routine liver resection is not recommended in patients with portal nodal disease, including radiologically suspicious portal nodes or malignant portal nodes found preoperatively or intraoperatively.
- Routine liver resection is not recommended in patients with non-pulmonary EHM.
- RCTs showed a trend in favour of perioperative chemotherapy that did not reach statistical significance. Additional trials are needed.
- The data suggest that patients who are initially unresectable may benefit from receiving chemotherapy to identify a subset of patients in whom successful conversion to resectability is achieved.
- Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and adequate functional liver can be left as a remnant.

PREPARATION OF SECTION 1 GUIDELINES AND RECOMMENDATIONS: ADDITIONAL LITERATURE REVIEW

METHOD

During the reading of the systematic review and preparation of the guideline recommendations by the Working Group, the Group determined that additional information from the included studies might be important in their interpretation. For the question on portal nodes, the study location (surgical centres), time period, macroscopic or microscopic involvement, and chemotherapy given were recorded. Some of the other studies were reexamined where the results appeared unclear or inconsistent.

RESULTS

Liver plus Pulmonary Resection

Fourteen studies with liver and lung resection were included in the systematic review. The median five-year survival was 31% (9% to 74%). The relatively high survival of 74% reported by Shah et al (6) was calculated from the date of the first metastasectomy instead of the second (usually pulmonary) metastectomy used in several other studies; however, the median overall survival was still 42.2 months after the last metastasectomy. Shah et al reported the use of aggressive surgical therapy plus pseudoadjuvant chemotherapy after liver resection (51% received 5FU or irinotecan). Recurrence was treated with repeated liver metastasectomy in seven patients (18%) and repeat lung resections in 12 patients (31%).

Portal Nodal Disease

One additional study was located from the reference lists. Data sorted by timing of detection are given in Table 1 (3,7-18). All studies included only small numbers of patients (n=7-35) over several years in a limited number of surgical centres in France (five studies), Japan (three studies), Germany (one study), and the United States (USA) (one study).

While five-year survival after liver resection was reported as 0% in some of the older studies, it was 12% to 33% in the five most recent studies (see Table 1). The three-year

survival was 27% to 56%. Adam et al (8) performed a resection in patients responding to or stabilized with preoperative chemotherapy and found five-year survival of 25% with pedicular node involvement, and 0% with celiac or para-aortic involvement. Adjuvant chemotherapy was routinely recommended. Jaeck et al (16) found 38% survival at three years when only Area I nodes were involved. A later study (15) found that the involvement of either Area 1 or Area 2 nodes resulted in much better survival than if both areas were involved (three-year survival of 36% for one area versus 18% for both areas; five-year survival of 26% versus 0%). Adjuvant chemotherapy based on pathologic examination and after multidisciplinary conference discussion was given in 36/45 patients; five-year survival was 23% versus 0% in those without adjuvant chemotherapy. The authors noted the evolution in treatment of colorectal liver metastases since their previous study, including perioperative chemotherapy and aggressive surgical resection (15).

Liver plus Other Metastases

The range in five-year survival for patients with resected liver metastases (no EHM present) was reported in six studies as 34% to 53%. Three year survival with liver plus EHM was 20% to 40% in most reported studies. Five year survival was 15% to 32%. Overall, these rates are about 30% to 50% of those found in patients with resected liver metastases but without EHM, though the data are not consistent across the various extrahepatic sites. For peritoneal metastases, Elias et al (9) reported three-year and five-year survival rates of 28% and 16%, respectively, while Carpizo et al (3) reported survival of 41% and 30%. Carpizo et al also found that ovarian metastases did not affect survival (five-year survival of 51% compared to 49% without EHM). Rees et al (19) reported on local infiltration to the diaphragm and other organs with a five-year survival of 34% and 30% (36% without EHM). In contrast, two studies reported 0% survival with para-aortic lymph node metastases.

Radiographic Complete Response (RCR) Following Chemotherapy

The studies involving liver resection after RCR are summarized in Table 2 (11, 20-23). The Auer et al study (24) was obtained from the authors but is excluded as it was not published until after the date of the literature search. The Elias studies (11,23) included one patient with 38 areas of LM, and Tanaka et al (22) included patients with one to 29 liver metastases. The other studies excluded patients with more than nine or ten liver metastases (20,21). Four of the studies administered chemotherapy by HAI to either some or all patients. Elias et al (23) found that recurrence is lower with HAI than with systemic treatment. Several articles on downstaging recommended limiting the duration of presurgical chemotherapy in order to minimize areas of liver metastases with RCR, which are then difficult to locate and resect (25-27).

Table 1: Outcomes for patients with portal nodal disease.

Author (Year)	Resection Date	Study or Author Location	Nodes Involved	# of Pts	Survival			Chemotherapy	Detection of Nodal Involvement
					Median, months	3-year (%)	5-year (%)		
Aoki et al. (2008)[7]	1988-2005	Tokyo, Japan	Positive + negative*	187	35	49	30	54% of patients, mostly older drugs	Preoperatively, intraoperatively (?)
			Hepatoduodenal ligament *	9	48	56	NR		
Adam et al (2008)[8]	1992-2006	Villejuif, France	Negative	710	65	68	53	Preoperative (oxaliplatin or irinotecan?)	Preoperatively or intraoperatively
			Pedicular †	26	30	-	25		
Carpizo et al (2009)[3]	1992-2007	New York, USA	Negative	1242	55	67	49	Some patients, better survival with irinotecan, oxaliplatin, biologicals vs. older agents (p=0.13)	Preoperatively or intraoperatively
			Hepatoduodenal ligament + hepatic artery	27	26	31	12		
Elias et al (2003)[9]	1987-2001	Villejuif, France	Negative	265	41	NR	34	About 1/2 received 5FU + folinic acid, +/- oxaliplatin or irinotecan	Intraoperatively, preoperatively (?). En bloc lymphadenectomy of suspected nodes
			Hepatoduodenal ligament	12	NR	27	27		
Elias et al (2004)[10,11] subset with R0	1987-2001	Villejuif, France	Negative	219	NR	56	33		
			Hepatoduodenal ligament	10	NR	33	33		
Kokudo et al (1999)[12]	1980-98	Tokyo, Japan	Negative	66	NR	NR	50	No, recommended for further studies	Intraoperatively but not preoperatively. At least one principle node resected in all patients since July 1995 (n=44).
			Hepatoduodenal ligament	9	NR	0	0		
Beckurts et al (1997)[13]	1987-94	Munchen, Germany	Negative	91	NR	48	22	Not mentioned	Preoperatively in 6 patients, routine lymphadenectomy in rest; mean 3 nodes in all patients
			Hepatoduodenal ligament	35	NR	3	0		
Nakamura et al (1999)[14]	1978-98	Hamamatsu-shi, Japan	Negative	36	NR	NR	43	Not mentioned	Lymphadenectomy in all patients 1978-89; patients with palpable nodes 1990-98
			Hilar nodes ‡	7	NR	33	33		
Oussoultzoglou et al (2009)[15]	2002-2006	Strasbourg Cedex, France	Area 1 § Area 2 § Area 1 and 2 §	17 10 18	19 20 20	34 40 18	26 27 NR	Oxaliplatin, Irinotecan, Bevacizumab or Cetuximab; better outcomes with chemo	Lymphadenectomy if suspicious nodes during laparotomy, or high risk of involvement. ¶ Not detected radiologically

Author (Year)	Resection Date	Study or Author Location	Nodes Involved	# of Pts	Survival			Chemotherapy	Detection of Nodal Involvement
					Median, months	3-year (%)	5-year (%)		
Jaeck et al (2002)[16]	1993-98	Strasbourg Cedex, France	Negative	143	52.8	62	46.7	Not mentioned	Lymphadenectomy in all patients, preoperative status not indicated
			Area I §	8	NR	38	NR		
Ambiru et al (1999)[17]	1984-97	Chiba, Japan	Negative	141	NR	45	27	Some patients	Routine lymphadenectomy; not detected by imaging
			Hepatoduodenal ligament	8	NR	13	13		
Laurent et al (2004)[18]	1985-2000	Bordeaux, France	Negative	133	45	56	43	About 1/2 patients received 5FU (older drugs), no effect	Lymphadenectomy of specific nodes (mean 3.3 nodes); only patients without macroscopic involvement
			Hepatic pedicle (sites 12a, 12b, 12p, 8a)	23	23	27	5		

Abbreviations: 5FU = 5-fluorouracil; Pts. = patients; vs. = versus; NR = not reported.

* Of the 187 patients, 37 had extrahepatic metastasis: 21 distant organs, 13 localized peritoneal seeding, and 9 hilar lymph nodes (includes 3 patients with other extrahepatic metastasis)

† Distal to the gastroduodenal artery branch; 8 patients also had lung metastasis

‡ Clearance (lymphadenectomy) of the hepatoduodenal ligament, retropancreatic, and celiac axis nodes

§ Lymphadenectomy of nodes in Area 1 (hepatoduodenal ligament and retropancreatic portion) and Area 2 (around the common hepatic artery and celiac axis; not part of the portal node definition)

¶ At least one of the following: >=3 liver metastases, metastasis in segments 4 or 5, or high CEA

Table 2: Liver metastases (LM) with radiographic complete response to preoperative chemotherapy (missing or disappearing lesions).

Study	Detection Method	Preoperative Chemotherapy	Patients with Radiographic Complete Response					Number of Persistent LM Observed / Total Monitored				LM with Complete Response *
			# Patients	# LM		# LM with RCR		Intra-operative	Pathology	Recurrence	Total	
				Total	Per Patient	Total	Per Patient					
Benoist et al, 2006[20]	CT + Ultrasound	FU+folinic acid +/- oxaliplatin or irotecan, systemic	38	183	< 10 mean 4.8±2.5	66	Mean 1.7	20/66 (37%)	12/15 (80%)	23/31 (74%)	55 (83 %)	11 (17%)
Fiorentini et al, 2008[21]	CT + Ultrasound	Floxuridine by HAI	48		< 9	106	Mean 2.2	52/106 (49%)	22/35 (63%)	33/106 1 yr (31%) 86/106 2 yr (81%)		20 (19%)
Tanaka et al, 2009[22]	CT	5FU + folinic acid + cisplatin by HAI (n=56); 13 also received oxiplatin systemically; 7 received only systemic treatment	23		Median 6 (1-29)	86	Mean 3.7	31 /86 (36%) †	11/45 (24%)†	11/27 (41%)†	42 (49%)	44 (51%)
								Patients with Persistent LM Observed / Total Monitored				Patients with Complete Response *
								Intra-operative	Pathology	Recurrence	Total	
Benoist et al, 2006[20]	CT + Ultrasound	FU+folinic acid +/- oxaliplatin or irotecan, systemic	38	183	< 10 mean 4.8±2.5	66	Mean 1.7	9/38 (24%)	12/15 (80%)	11/14 (79%)	32 (84%)	6 (16%)
Elias et al, 2004[11]	CT + MRI + Ultrasound ‡	5FU+oxaliplatin or irinotecan by IV (n=6); systemic chemo +oxiplatin by HAI (n=5)	11 (+4) ‡	109	Median 7 Mean 9.9 (2-12, 38 in one patient)	54 ‡	Median 2 Mean 4.9 (1-3, 37 in one patient)	4/15 (27%)	6/11 (55%)	3/11 (27%)	11/15 (73%)	4 (27%)
Elias et al, 2007[23] (overlaps Elias 2004)	CT + MRI + Ultrasound	Folinic acid, 5FU, oxaliplatin, or irinotecan: systemic or by HAI	16	134	Median 6 Mean 8.4 (2-12, 38 in one patient)	69	Median 2 Mean 4.3 (1-6; 11, 32 in one patient each)	Excluded	Excluded if excised	6/16 (38%)	6/16 (38%)	10 (62%)

* No tumour detected interoperatively or by pathological exam of resected tissue and no recurrence at the site on follow-up.

† Of 31 LM with macroscopic residual metastases observed by laparotomy, 14 were treated by microwave ablation and the other 17 resected; of those resected 11 had viable tumour cells and 6 had no viable tumour cells. Of 55 LM with no macroscopic residual metastases, liver resections included the sites of 28 and no viable tumour cells found, while 27 left in place resulted in 11 recurrences in situ.

‡ 4 of the 15 patients had disappearing LM located interoperatively and were excluded from the study. The number of lesions is only for the 11 other patients. Missing LM were defined as those missed by at least one of the imaging techniques (CT, MRI and/or ultrasound). Only 5 patients had at least one LM missed by all three techniques.

CLINICAL TRIALS IN PROGRESS

Clinical trial registries at the US National Institutes of Health (NIH) (http://clinicaltrials.gov, http://www.cancer.gov/clinicaltrials) (28,29) were searched for ongoing or recently completed Phase III chemotherapy trials that met the scope of the review. These studies are detailed in Appendix 2. Three studies involve neoadjuvant chemotherapy: one study from China reporting on neoadjuvant XELOX (oxaliplatin plus capecitabine) and two studies from the US comparing perioperative (neoadjuvant plus adjuvant) to adjuvant chemotherapy (FOLFOX4 in China; mFOLFOX6 or FOLFIRI in the US). In addition, another study compares perioperative chemotherapy with and without cetuximab, one compares adjuvant oxaliplatin and capecitabine to follow-up, and the rest compare various regimens of adjuvant chemotherapy. There are also several other ongoing Phase II trials in the registry that compare various chemotherapy agents for neoadjuvant or adjuvant use (Question 2a), and some additional non-randomized studies on conversion therapy (Question 2b).

CONCLUSIONS

The conclusions reached after this reevaluation of the studies are those given in Section 1: Guideline Recommendations.

CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3.

ACKNOWLEDGEMENTS

The authors would like to thank the following participants in the guideline development process:

- Hans Messersmith, Assistant Director, PEBC
- Sheila McNair, Assistant Director, PEBC
- Carol De Vito, Documents Manager, PEBC
- Amber Hunter, Manager, Surgical Oncology Program, CCO

REFERENCES

1. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery 2012; 151(6):860–70. Epub 2012 Feb 7. doi: 10.1016/j.surg.2011.12.01
2. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.biomedcentral.com/1471-2288/7/10
3. Carpizo DR, Are C, Jarnagin W, DeMatteo R, Fong Y, Gönen M, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol. 2009;16(8):2138-46.
4. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Peri-operative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007-16.
5. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26(30):4906-11.
6. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg. 2006; 202(3):468-75.
7. Aoki T, Umekita N, Tanaka S, Noda K, Warabi M, Kitamura M. Prognostic value of concomitant resection of extrahepatic disease in patients with liver metastases of colorectal origin. Surgery. 2008;143(6):706-14.
8. Adam R, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol. 2008;26(22):3672-80.
9. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg. 2003;90(5):567-74.
10. Elias D, Sideris L, Pocard M, Ouellet JF, Boige V, Lasser P, et al. Results of R0 resection for colorectal liver metastases associated with extrahepatic disease. Ann Surg Oncol. 2004;11(3):274-80.
11. Elias D, Youssef O, Sideris L, Dromain C, Baton O, Boige V, et al. Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. J Surg Oncol. 2004;86(1):4-9.
12. Kokudo N, Sato T, Seki M, Ohta H, Azekura K, Ueno M, et al. Hepatic lymph node involvement in resected cases of liver metastases from colorectal cancer. Dis Colon Rectum. 1999;42(10):1285-91.
13. Beckurts KT, Hölscher AH, Thorban S, Bollschweiler E, Siewert JR. Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. Br J Surg. 1997;84(8):1081-4.
14. Nakamura S, Suzuki S, Konno H. Resection of hepatic metastases of colorectal carcinoma: 20 years' experience. J Hepatobiliary Pancreat Surg. 1999;6(1):16-22.
15. Oussoultzoglou E, Romain B, Panaro F, Rosso E, Pessaux P, Bachellier P, et al. Long-term survival after liver resection for colorectal liver metastases in patients with hepatic pedicle lymph nodes involvement in the era of new chemotherapy regimens. Ann Surg. 2009;249(6):879-86.

16. Jaeck D, Nakano H, Bachellier P, Inoue K, Weber JC, Oussoultzoglou E, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. Ann Surg Oncol. 2002;9(5):430-8.
17. Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, et al. Hepatic resection for colorectal metastases: Analysis of prognostic factors. Dis Colon Rectum. 999;42(5):632-39.
18. Laurent C, Sa Cunha A, Rullier E, Smith D, Rullier A, Saric J. Impact of microscopic hepatic lymph node involvement on survival after resection of colorectal liver metastasis. J Am Coll Surg. 2004;198(6):884-91.
19. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247(1):125-35.
20. Benoist S, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006;24(24):3939-45.
21. Fiorentini G, Del Conte A, De Simone M, Guadagni S, Mambrini A, D'Alessandro M, et al. Complete response of colorectal liver metastases after intra-arterial chemotherapy. Tumori. 2008;94(4):489-92.
22. Tanaka K, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. Ann Surg. 2009;250(6):935-942.
23. Elias D, Goere D, Boige V, Kohneh-Sharhi N, Malka D, Tomasic G, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. Ann Surg Oncol. 2007;14(11):3188-3194
24. Auer RC, White RR, Kemeny NE, Schwartz LH, Shia J, Blumgart LH, et al. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. Cancer. 2010;116(6):1502-9.
25. Nuzzo G, Giuliante F, Ardito F, Vellone M, Pozzo C, Cassano A, et al. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. J Gastrointest Surg. 2007;11:318-24.
26. Skof E, Rebersek M, Hlebanja Z, Ocvirk J. Capecitabine plus irinotecan (XELIRI regimen) compared to 5-FU/LV plus irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. BMC Cancer [Internet]. 2009;9(120). Available from: http://www.biomedcentral.com/1471-2407/9/120
27. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Ann Surg. 2009;249(3):420-5.
28. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine, U.S. National Institutes of Health (NIH). 2000 Feb 29 [cited 2010 Nov]. Available from: http://clinicaltrials.gov/
29. ClinicalTrials [Internet]. Bethesda (MD): National Cancer Institute, U.S. National Institutes of Health (NIH). [cited Nov 2010]. Available from: http://www.cancer.gov/clinicaltrials

Appendix 1. AMSTAR rating of systematic review.

1. Was an 'a priori' design provided? **Yes**

2. Was there duplicate study selection and data extraction? **Yes**
   (Second reviewer in cases of uncertainty)

3. Was a comprehensive literature search performed? **Yes**
   (Text, MESH, and Embase terms given; search strategy not provided; consulted reference lists and content experts)

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? **Yes**
   (only fully-published English language reports)

5. Was a list of studies (included and excluded) provided? **Yes/No**
   (not provided, but stated it is "available upon request")

6. Were the characteristics of the included studies provided? **Some (Yes/No)**
   (number of patients, survival, chemotherapy for Question 2; other data necessary for interpretation was missing)

7. Was the scientific quality of the included studies assessed and documented? **No**
   (only RCT or case series, minimum patient numbers specified)

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? **No**

9. Were the methods used to combine the findings of studies appropriate? **Not applicable**

10. Was the likelihood of publication bias assessed? **Not applicable**

11. Was the conflict of interest stated? **No**

Appendix 2. Phase III clinical trials in progress (clinicaltrials.gov/ (28), Clinical Trials, NCI database (29)).

NCT ID, other ID	Stage	Trial Location	Brief and Official Titles of Trials
Neoadjuvant (before resection)			
NCT00630045, OXALIC	Recruiting	China	Phase 3 Study of Surgery Combined With Neoadjuvant Chemotherapy(XELOX) in Colorectal Cancer With Resectable Liver Metastasis
			A Phase III Study of Surgery in Combination With Neoadjuvant Chemotherapy of Oxaliplatin Plus Capecitabine in Colorectal Cancer With Resectable Liver Metastasis
Neoadjuvant + Adjuvant (Perioperative) vs. Adjuvant			
NCT01189227, NSABP-C-11	Complete (Dec 2011)	United States	Combination Chemotherapy Before or After Surgery in Treating Patients With Colorectal Cancer With Liver Metastases That Could Be Removed By Surgery
			Phase III Randomized Study of Postoperative Versus Perioperative Chemotherapy in Patients With Potentially Resectable Hepatic Colorectal Metastases
NCT01035385	Recruiting	China	Compare FOLFLOX4 in Preoperative and Postoperative and Postoperative in Resectable Liver Metastasis Colorectal Cancer (MCC)
			Phase III Study to Compared Preoperative and Postoperative With FOFLOX4 Chemotherapy and Postoperative With FOFLOX4 Chemotherapy in Patients With Resectable Liver Metastasis From Colorectal Cancer
Neoadjuvant + Adjuvant (Perioperative)			
NCT00482222, USCTU-4351, USCTU-EPOC	Recruiting	United Kingdom	Combination Chemotherapy With or Without Cetuximab Before and After Surgery in Treating Patients With Resectable Liver Metastases Caused By Colorectal Cancer
			A Prospective Randomised Open Label Trial of Oxaliplatin/Fluoropyrimidine Versus Oxaliplatin/Fluoropyrimidine Plus Cetuximab Pre and Post Operatively in Patients With Resectable Colorectal Liver Metastasis Requiring Chemotherapy
Adjuvant			
NCT00394992, HEPATICA	Recruiting	Netherlands	Adjuvant Xeloda Plus Eloxatin +/- Avastin After Radical Resection of Liver metastasis of Colorectal Cancer
			Randomized Phase III Study Post Radical Resection of Liver Metastasis of Colorectal Cancer: Bevacizumab in Combination With XELOX as Adjuvant Chemotherapy vs. XELOX Alone
NCT00869271, 2009-01	Completed	China	Postoperative Folfox4 Only Versus Folfox4 Plus Transhepatic Arterial Chemotherapy (TAC) in the Treatment of Unresectable Liver Metastasis of Colorectal Cancer
			Postoperative Folfox4 Only vs. Folfox4 Plus TAC in the Treatment Unresectable Liver Metastasis of Colorectal Cancer: a Randomized Prospective Control Trial
NCT00156975, ADHOC	Active (Closed to recruitment)	Germany	Oxaliplatin and Capecitabine Versus Follow-up After Resection of Colorectal Liver Metastases
			Adjuvant Chemotherapy With Oxaliplatin and

NCT ID, other ID	Stage	Trial Location	Brief and Official Titles of Trials
			Capecitabine Versus Follow-up After Resection of Colorectal Liver Metastases- Randomized Phase III Study
NCT00143403, CPT-GMA-301	Completed	Europe, Asia, South Africa	Comparing Irinotecan and 5 FU/FA To 5-FU/FA After Resection Of Liver Metastases For Colorectal Cancer
			Multi-Centre Phase III Open Label Randomized Trial Comparing CPT-11 In Combination With A 5-FU/FA Infusional Regimen To The Same 5-FU/FA Infusional Regimen Alone, As Adjuvant Treatment After Resection Of Liver Metastases For Colorectal Cancer
NCT00268398, GERCOR-C02-1	Completed *J Clin Oncol 30, 2012 (suppl; abstr 3506)*	France	Combination Chemotherapy in Treating Patients With Colorectal Cancer and Liver Metastases
			Essai De Phase III De Chimiotherapie Par FOLFOX 4 Ou Par Une Succession FOLFOX 7 - FOLFIRI Chez Des Patients Ayant Des Metastases Resecables D'Origine Colorectale - MIROX
			Phase III Randomized Study of Oxaliplatin, Fluorouracil, and Leucovorin Calcium (FOLFOX 4) Versus High-Dose Oxaliplatin, Fluorouracil, and Leucovorin Calcium (FOLFOX 7) Followed by Irinotecan Hydrochloride, Fluorouracil, and Leucovorin Calcium (FOLFIRI) in Patients With Colorectal Cancer Metastatic to the Liver
Initially Unresectable			
NCT00610636, 9100015204	Recruiting	Taiwan	Treatment Outcomes of Hepatic Metastasis After FOLFOX-4 Therapy
			Oncologic Outcomes of Surgical Versus Non-Surgical Methods for the Treatment of Resectable Colorectal Liver-Confined Metastases Converted From Initially Non-Resectable Metastases by FOLFOX-4 Neoadjuvant Chemotherapy: A Randomized Clinical Trial

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 17-7: Section 3

The Role of Liver Resection in Colorectal Cancer Metastases: EBS Development Methods and External Review Process

Steven Gallinger, James J. Biagi, Glenn G. Fletcher, Cindy Nhan, Leyo Ruo, Robin S. McLeod, and the Expert Panel

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

Report Date: June 15, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) and the Surgical Oncology Program (SOP) are initiatives of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care. The mandate of the SOP is to continually improve the quality and accessibility of cancer surgery across Ontario. The SOP and PEBC have worked collaboratively on a number of occasions to develop evidence-based materials relevant to the surgical community in Ontario.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

As part of its quality improvement mandate, the SOP works with surgeons to identify knowledge gaps and problems in the organization and delivery of services, develops indicators to measure performance, supports local champions and fosters communities of practice. As cancer surgery is performed at both academic and community hospitals, surgeons across the province participate in expert panels along with other clinicians, health care administrators, other health care professionals, and methodologists as needed for specific quality initatives including guidelines.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

The CCO SOP considered this topic to be of high priority because of advances in chemotherapy and expanding indications for liver resection. A working group of clinical experts was established to prepare a systematic review on the role of liver resection for colorectal cancer metastases. The PEBC was then contacted to continue the process by preparing a practice guideline based on this systematic review, including the regular internal and external review process, professional consultation, and knowledge dissemination. The final version of the systematic review incorporated feedback obtained during the guideline development process.

This EBS was developed by the Working Group and the Expert Panel which were constituted for the development of this guideline. The series 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. A list of the Working Group and Expert Panel members is given in the Appendix at the end of Section 1. The participants represented the various sites in Ontario designated as HPB surgical centres meeting the Standards set by CCO. HPB surgeons and medical oncologists were part of the Working Group, while the Expert Panel also included radiologists, general surgeons, and a thoracic surgeon.

Report Approval Panel:

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The report was approved by the RAP with the following suggestions for minor changes and the Working Group responses:

Section 1

- Background: It was suggested that this section be more succinct.
  - The authors shortened the section and reformatted it for better readability.

- 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.
  - The authors added text in the Background to this effect. The authors note that several of the Qualifying Statements or Key Evidence statements indicate that the

evidence is limited and based on non-controlled trials (retrospective/prospective series or cohorts). Wording in Question 2a on perioperative chemotherapy has been altered to clarify that these RCTs showed trends but these were not statistically significant. A table has been added to Section 2 of the Guideline which lists some of the RCTs currently in progress.

- Recommendations and Key Evidence 2a) It was suggested to remove details of the case series studies in the Key Evidence as there were RCTs.
  - The authors edited this section.

- The authors should be careful and review specifics of language that is associated with implications of a comparison. Given the context of a PEBC document, "improved" suggests a comparison and by definition, case series do not provide this.
  - Reformatting the Background and adding a paragraph on the role of liver resection with respect to long-term survival provide a better framework for the guideline. This information was in the Review article on which the Guideline is based but had not been included in Section 1. Key Evidence of Question 1A noted by the reviewer was reworded for both accuracy and clarity. Minor changes were incorporated for some of the other questions.

- The second qualifying statement in Part 2A (perioperative chemotherapy) related to the Sargent citation appears to be overstated. These populations are very different and taking data from the adjuvant situation and considering these for the population associated with this guideline may be more so regarded as hypothesis-generating as opposed to generalizability. The word "*reasonably*" appears to overstate generalizability. At a methodologic level, the authors should expand upon the implications of "*even higher absolute risk reduction benefit*". Given the much poorer outcome of the patient population considered in this guideline, as compared with those receiving adjuvant chemotherapy, even large reductions in the HR (as compared with those seen in RCTs testing adjuvant therapy) may be associated with relatively marginal absolute gains in time-dependent endpoints. This risk is particularly so given the lack of quality data on overall survival (at least pending any follow-up reporting of the EORTC trial).
  - The Qualifying Statement has been modified to reflect current practice, and discussion of the magnitude of the risk reduction was removed.

- The report does not differentiate management, especially perioperative neo/adjuvant chemotherapy, for patients who have or have not received adjuvant chemotherapy at the time of their initial diagnosis. The authors should consider whether this deserves comment.
  - Details of the RCTs on chemotherapy were added to the Key Evidence for Question 2A on perioperative chemotherapy. Qualifying statements were added indicating that perioperative chemotherapy prior to liver resection should be of limited duration (six weeks). Further management details should be on an individual basis and discussed at the MCCs.

Section 2

- Introduction: It was suggested that details of the AMSTAR rating be given.
  - The authors added Appendix I containing a summary of the questions and ratings.

- Additional Review of the Literature - Method: It was suggested that this section be more succinct.
  - The authors of the systematic review revised the draft of their manuscript, resulting in the elimination of most of the discrepancies and additional information needs noted in the draft of the guideline seen by RAP. Section 2 of the guideline was shortened and modified to be consistent with the revised systematic review.

External Review by Ontario Clinicians and Other Experts

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

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, Sections 1 and 2 were circulated to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Expert Panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review February 9, 2012)

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 (EHM)?

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) following chemotherapy?

TARGET POPULATION

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 extrahepatic metastasis with curative intent.

RECOMMENDATIONS AND KEY EVIDENCE

The report "Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards," a special report of CCO/PEBC (16) provides standards for the management of primary and secondary liver cancer in Ontario. These requirements 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 that has appropriate physical resources (diagnostic equipment, operating rooms, intensive care unit [ICU]), staffing (surgeons with advanced training in HPB surgery, nurses, radiologists, medical and radiation oncologists), and a high volume of HPB surgeries (a minimum of 50 index HPB cases per year).

1. What is the role of liver resection in patients with extrahepatic metastases (EHM)?

1a) Pulmonary Metastases
Recommendation

Patients with liver and lung metastases should be seen in consultation by 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 previous 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 (13)). In studies with combined liver and lung resection, three year survival was 36-59%, and five year survival was 9-74%.

- The relatively high survival of 74% reported by Shah et al (31) was calculated from the date of the first metastasectomy instead of the second (usually pulmonary) metastectomy 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. Shah et al (31) reported the use of aggressive surgical therapy plus pseudoadjuvant chemotherapy (after potentially curative metastasectomy) following the liver resection (51% received 5-fluorouracil or irinotecan). Recurrence was treated with repeated liver metastasectomy in seven patients (18%) and repeat lung resections in 12 patients (31%).

Qualifying Statements

While the literature review tabulates the numbers of cases by the order of resection (in some studies, the data are actually for the occurrence of metastases), most of the original publications do not subdivide survival data according to the timing of resection. The order of surgery is often a reflection of 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 metastectomy was performed first. Shah et al (31) indicate that this was to maintain pulmonary reserve and rule out unexpected extrahepatic abdominal disease; lung resection was performed six weeks later. Patients with either 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 metastectomy should not exclude the resection of new metastases.

1b) Portal Node Metastases

Definition

Portal nodes are defined in the literature review as those lymph nodes that are found in the hepatoduodenal ligament. Jaeck et al (32) divide the hepatic pedicle lymph nodes into Area 1 (hepatoduodenal ligament and retropancreatic portion) and Area 2 (around the common hepatic artery and celiac axis).

Recommendation

***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, along with chemotherapy (oxaliplatin, irinotecan, and/or targeted therapy combinations), may be an option, after a full discussion with patients, in cases with limited nodal involvement and metastases that can be completely resected. Chemotherapy is discussed in Question 2 (see qualifying statements).**

Key Evidence

- Patients with portal nodal disease have a worse prognosis than do those without EHM (see Table 1 in Section 2).

- While five-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). The three-year survival was 27-56%.

- Adam et al (33) performed resections in patients responding to or stabilized with preoperative chemotherapy and found a five-year survival of 25% with pedicular node involvement, and 0% with celiac or para-aortic involvement.

- A later study by Jaeck's group (34) found that the involvement of either Area 1 or Area 2 nodes resulted in much better survival than if both areas were involved (three-year survival 36% for one area versus 18% for both areas; five year survival 26% versus 0%); adjuvant chemotherapy was an independent predictor of overall survival in multivariate analysis. They noted the evolution in treatment of colorectal liver metastases since their previous 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/selected nodes), use and type of chemotherapy, and presence of other EHM are not consistent across the studies. Five-year follow-up is incomplete in several publications. Some studies conclude that portal nodal involvement should not be considered an absolute contraindication for the resection of colorectal liver metastases. The improvement in surgical techniques, preoperative treatment, and 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. While Adam et al (33) used this criterion in their study, presumably based on their previous results (35), other publications concluded the response to neoadjuvant chemotherapy did not correlate with overall survival (36). No consensus was reached on this issue.

1c) Metastases at Other Sites

Recommendation

***Routine* liver resection is not recommended in patients with non-pulmonary EHM. Liver plus extrahepatic resection along with chemotherapy (oxaliplatin, irinotecan and/or targeted therapy combinations) may be an option, after full discussion with patients, for metastases that can be completely resected. Chemotherapy is discussed in Question 2 (see qualifying statements).**

Key Evidence

- Three-year survival following resection of liver plus EHM is 20% to 40% in most reported studies (see Table 3 of the review by Quan et al (13)). Five-year survival is 15% to 32%. Overall these rates are one third to one half of those found in patients with resected liver metastases but without EHM, though data are not consistent across the various extrahepatic sites.

- For peritoneal metastases, Elias et al (37) reported three-year and five-year survival rates of 28% and 16%, while Carpizo et al (38) reported survival rates of 41% and 30%.

- Carpizo et al (38) also found that ovarian metastases did not affect survival (five-year survival of 51% compared to 49% without EHM).

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

- Several publications by Elias et al (37,39,40) form the basis of the consensus of the European Colorectal Metastases Treatment Group (20), 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 (41) 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

There appears to be an increasing number of institutions performing combined liver resection and resection of EHM, although the evidence on outcomes is heterogeneous. The definitions for the site of disease, presentation of disease, and type of surgery performed differ among studies. Only four studies (see Table 3 in the review (13)) reported separate data for multiple extrahepatic sites other than the hepatic lymph nodes.

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

2a) Resectable disease: Does perioperative chemotherapy result in an improved outcome in patients having liver resection for CRC metastases?

Recommendation

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 EORTC Intergroup trial 40983 reported by Nordlinger et al (42) is a multicentre RCT comparing chemotherapy plus liver resection (6 cycles of FOLFOX4 before and 6 cycles after surgery) to surgery alone. While 42% of the patients had previously received non-oxaliplatin adjuvant chemotherapy for the primary cancer, patients who had received oxiplatin prior to the trial start were excluded. The study was closed early (235 events accrued instead of the planned 278 events) as "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), there was a 7.3% improvement in PFS at three years in the surgery plus chemotherapy group, a trend that was not statistically significant (hazard ratio [HR], 0.79; confidence interval [CI], 0.62 to 1.02; p=0.058). The median PFS was 18.7 months versus 11.7 months without chemotherapy. Reanalysis of the subset of patients who received resection indicated a significant increase in PFS (HR, 0.73; CI, 0.55 to 0.97; p=0.025).
    - Reversible postoperative complications occurred more often after chemotherapy than with surgery alone (25% versus 16%; p=0.04).
    - Perioperative chemotherapy reduced the risk of relapse by one quarter.

- The only other randomized trials are reported by Mitry et al (43) as a pooled analysis of two smaller studies (FFCD Trial 9002 and ENG Trial) of 5-fluorouracil (5FU) postoperative chemotherapy that were both stopped early due to slow accrual. The FFCD trial excluded patients who had received chemotherapy in the year preceding liver surgery, while the ENG trial excluded patients with prior chemotherapy for metastatic disease or metastases diagnosed within six months of completion of adjuvant chemotherapy for the primary tumour. There were trends in PFS and overall survival favouring the surgery plus chemotherapy group (median overall survival, 62.2 versus 47.3 months; p=0.095) that did not reach statistical significance.

- The 28 case series (see Table 4 in the review by Quan et al (13)) were heterogeneous in

regimens and outcomes. Preoperative chemotherapy-induced liver damage (CILD) was identified in some of the studies.

- Practice standards and guidelines support chemotherapy in metastectomy patients.
  - An expert panel of the European Colorectal Metastases Treatment Group (including several participants of the EORTC 40983 trial) recommends 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"(44).
  - The Advanced Colorectal Cancer: ESMO Clinical Practice Guidelines supports the use of perioperative chemotherapy (18).
  - NCCN practice guidelines for colon and rectal cancers also support chemotherapy plus resection for metastases (45,46).

Qualifying Statements

While results from confirmatory trials are awaited, the results from current evidence demonstrate consistent trends that favour perioperative chemotherapy, to the extent that there has been a widespread change in practice provincially and across other jurisdictions for the routine use of perioperative chemotherapy.

In stage 3 and high-risk stage 2 primary CRC, there is a well-known one-third relative risk reduction in recurrence with the use of adjuvant chemotherapy (47). Clinicians have therefore extrapolated that patients with resected metastatic disease are likely to benefit.

The most widely recommended perioperative chemotherapy is an oxaliplatin-based combination. It is well-established that chemotherapy exposure results in CILD or changes to the liver parenchyma. Differences in surgical outcomes resulting from different types of liver damage have been reported between irinotecan and oxaliplatin combination therapies and these differences have led to the preferential use of oxaliplatin-based combinations. In the appropriate settings, an irinotecan-based combination or fluoropyrimidine monotherapy may be reasonable alternatives.

Most studies recommend that the duration of preoperative chemotherapy be limited. Liver toxicity and radiographic complete response (see Question 3) are more likely after prolonged exposure. Karoui et al (48) found increased morbidity among patients with six or more cycles of chemotherapy, and the Nordlinger et al trial (42) limited preoperative chemotherapy to six cycles. Most of the preoperative chemotherapy studies for initially unresectable metastases (Question 2b) performed repeat imaging during chemotherapy with resection as soon as was technically feasible (49-51).

Although there are fewer published data on resectable extrahepatic metastatic disease, the recommendations of perioperative chemotherapy extend to this patient population. 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.

2b) Initially unresectable disease: Should liver resection be performed in patients with initially unresectable metastatic liver disease following conversion chemotherapy?

Recommendation

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

Key Evidence

- The data suggest that patients who are initially unresectable may benefit from receiving chemotherapy in order to identify a subset of patients in whom successful conversion to resectability is achieved. In patients without EHM, preoperative chemotherapy gave 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 (13)).

- This 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 (41).

- Survival rates after conversion chemotherapy plus liver resection was 52-100% at three years (five studies) and 33-43% at five years (three studies), similar to rates in patients considered resectable without chemotherapy

Qualifying Statements

This question dealt primarily with CRC metastases only to the liver. Some of the patients in the reported studies had liver plus EHM, and the recommendations for Question1c would apply in these cases.

While multiple studies have suggested that some patients can be made resectable via chemotherapy, there are no RCTs, and these studies are largely case series. Different definitions of resectable were used. There is no expectation that an RCT with a non-surgical arm will be initiated in this patient population. Nonetheless, the data point to the potential for long term survival that has resulted in strong consensus in the oncology community for the widespread adoption of conversion chemotherapy with surgical intent.

Prolonged chemotherapy can result in liver toxicity (see Question 2a), surgical complications, and RCR (see Question 3). Most of the studies of preoperative chemotherapy for initially unresectable metastases used repeat imaging during chemotherapy with resection as soon as was technically feasible (49-51).

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

Recommendation

Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and 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 these patients. Close follow-up of the lesion with RCR is warranted to allow localized treatment or further resection for an in-situ recurrence.

Key Evidence

- Studies by Benoist et al (52), Fiorentini et al (53), and Tanaka et al (54) (see Table 2 in Section 2) give the proportion of liver metastases with RCR located intraoperatively (37%, 49%, and 36%, respectively), found by pathologic 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 (52) and Elias et al (39) reported that 16% and 27%, respectively, of *patients* had a true complete response.

- Postoperative chemotherapy was given in all except one study (not mentioned by Fiorentini et al (53)) 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 hepatic arterial infusion (HAI) to either some or all patients. Elias et al (55) found lower recurrence with HAI than with systemic treatment.

Qualifying Statements

These 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 those that were left in place. The extrapolation of data from

other studies suggests that resection would improve survival. Several articles on downstaging recommend limiting the duration of presurgical chemotherapy in order to minimize areas of liver metastases with RCR, which are then difficult to locate and resect (49-51). These studies used repeat imaging during chemotherapy with resection as soon as was technically feasible.

Methods

Targeted Peer Review: During the guideline development process, five targeted peer reviewers from Ontario and Alberta considered to be clinical and/or methodological experts on the topic were identified by HBP Surgical Oncology working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 9, 2012. Follow-up reminders were sent at two weeks and at four weeks. The HBP Surgical Oncology working group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals in Ontario who are the intended users of the guideline. The survey was distributed by email to 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 (GI) interest/expertise, and general surgeons with GI interest (subscribers to the CRC listserv).

Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on February 9, 2012. The consultation period ended on March 18, 2012. The HBP Surgical Oncology Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from the reviewers. The fourth reviewer had to decline due to other commitments. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the Targeted Peer Reviewer Questionnaire.

		Number of Reviewers for Each Rating (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(3.5)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**	0	0	0	0	2	1
2. **Rate the guideline presentation.**	0	0	0	0	1	2
3. **Rate the guideline recommendations.**	0	0	0	1	1	1
4. **Rate the completeness of reporting.**	0	0	0	0	2	1
5. **Does this document provide sufficient information to inform your decisions? If not, what areas are missing?**	0	0	0	0	2	1
6. **Rate the overall quality of the guideline report.**	0	**0**	0	0	1	2
	Strongly Disagree (1)	(2)	Neutral (3)		(4)	Strongly Agree (5)
7. **I would make use of this guideline in my professional decisions.**	0	0	0	0	1	2
8. **I would recommend this guideline for use in practice.**	0	0	0	0	1	2

9. **What are the barriers or enablers to the implementation of this guideline report?**
   - This is a complex disease process with ever changing data. The guideline will need regular updating. However, it does bring some order to the current chaos.
   - I see the main barrier as access to appropriate HPB centres where such evaluations can be properly done.
   - No major obstacles outside of need to refer some patients to centres offering liver resection- the machinery for this needs to be in place.

Summary of Written Comments

1. Would have liked to have seen some discussion of costs and risks of other options (i.e., chemotherapy).
2. One area not addressed was the approach to synchronous liver metastases and the timing of chemotherapy/resection of liver.
3. Only issue not clear is how to stage these patients, especially those that might be candidates for resection in setting of EHM or portal dx - role of PET?
4. I disagree with recommendation 2A as I do not feel there is sufficient evidence to make such a strong recommendation in favor of chemotherapy based upon current evidence (and even though it is widely practiced). Also think we need to consider synchronous where patients may never have had chemotherapy and metachronous where they may already have received adjuvant chemotherapy differently. Also for 2B the recommendation is [perhaps deliberately] vague about what to do about post-op chemotherapy in patients who receive downstaging to achieve resectability. There is really no clear evidence on this although it may be reasonable to recommend that a total of 6 months of chemotherapy be given (based on current adjuvant data).

Professional Consultation: Twenty-three responses were received. Key results of the feedback survey are summarized in Tables 2 and 3.

Table 2. Responses to four items on the Professional Consultation Survey.

Reviewers	# Sent	# Replies	# Declined*	# Completed Survey	% Completed
HPB CoP	19	3	1	2	10
Surgical Leads	13	5	2	3	23
Thoracic CoP	47	5	3	2	4
Medical Oncologists	42	10	4	6	14
General Surgeons	109	11	1	10	9
Total	230	34	11	23	10

* 1 on maternity leave, 1 too busy, 9 not an area of interest

Table 3. Number (%) of respondents in each rating category.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	**0**	1 (4)	10(43)	12 (52)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	1 (4)	11 (48)	11 (48)
3. I would recommend this guideline for use in practice.	0	0	0	9 (39)	23 (61)

4. What are the barriers or enablers to the implementation of this guideline report?

Enablers

- Multidisciplinary conferences with HPB specialists present to discuss surgical options for liver disease.
- Dissemination of guideline, encouraging tumour board discussion of stage 4 cases to ensure appropriate selection and referral.

Barriers

- Patients with Liver CRC metastases are not being referred for surgical resection. Belief in report by surgeons with nihilistic approach to metastatic colorectal cancer. Perceived paternalism.
- Lack of access to multi-disciplinary teams (MDT). Lack of financial support to participation in MDT. Access for remote patients to tumour board review and HPB assessment. The subject matter is by definition not straight forward and multi-disciplinary decision making is crucial.
- Access to facilities capable of metastatectomy. Accessibility of tertiary providers for surgical care is a barrier.
- Dissemination of information. Getting the information to the entire province of health care providers. Awareness is main barrier.
- Lack of RCTs or really good evidence for most of the issues addressed. Many "unique"

situations that don't fall neatly into a guideline on resections.
- Evidence is still confusing regarding the use of up front chemotherapy before resection of primary colon cancer in the setting of liver metastases

Summary of Written Comments

1. In recommendation 1b, where does the recommendation for "+/- targeted therapy" come from?
2. 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.
3. 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.
4. I think that both perioperative chemo and post operative chemo can be considered equally for the section on perioperative chemo for resectable liver disease.
5. Some Q and A with typical scenarios will help practicing surgeons better understand the guidelines.
6. I believe wording of a few of the recommendations should be changed. The caveat that resection can occur after discussion with the patient is in the wrong location. It would be more practical if the recommendation said: "currently resection of extrahepatic metastases is not a recommendation, however, there is a growing body of evidence that supports resection for some patients."

Modifications/Actions

Targeted Peer Review

1. A discussion of costs and risks of other options was considered to be outside the scope of this document. It is noted in the introduction that liver resection is the most effective treatment that achieves long-term survival and that offers the possibility of cure in stage IV disease limited to the liver.
2. Very little data is available on synchronous liver metastases and the timing of chemotherapy/resection of liver. A note on synchronous metastases was placed in the introduction. This was outside the scope of the document.
3. Staging should be done as part of the presurgical evaluation and discussed in MCC. This is indicated in the introduction. Methods of staging are outside the scope of the review.
4. The authors felt that recommendation 2A is valid, despite the limited evidence. The recommendation should be read in conjunction with the qualifying statements. The qualifying statements were revised in response to the comment.

Professional Consultation:

1. Listing of chemotherapy agents, included targeted therapies, was deleted in Recommendations 1b and 1c, and replaced with "perioperative systemic therapy". The qualifying statements for 2a were modified.
2. The authors agreed that the original statement is valid, though we adapted the wording slightly as a result of the comment.
3. As indicated in Section 2, studies evaluating HAI as a technique were outside the scope of the literature review, though RCTs comparing different chemotherapy agents

administered by HAI were included. A comment and about treatment of patients previously receiving adjuvant therapy was added to the qualifying statements for Question 2a.

4. Perioperative chemotherapy, defined as either before and after resection, or after resection was recommended. There are limited studies addressing the issue of the optimal timing of chemotherapy.
5. It was felt that a question and answer section was not within the role of a guideline.
6. We believe our intent and that of the reviewer are the same. We prefer to leave it as written. It is possible the reviewer missed the word "Routine", which is essential to the recommendation.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors and external reviewers were asked to disclose potential conflicts of interest. One of the authors (SG) received HPB Fellowship Support from Sanofi and from Roche. The other authors reported that they had no conflicts of interest. One external reviewer indicated that he had written an editorial/opinion piece and helped organize a consensus conference on this topic. The COIs 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. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002 Sep;13(9):1507-9; author reply: 1509.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.