Standards of care for curative surgery and management of metastatic colorectal cancer

REPORT FROM THE COLORECTAL CANCER ASSOCIATION OF CANADA CONSENSUS MEETING, MONTREAL, QUÉBEC, APRIL 24, 2010

Corresponding author: Scott Berry, MD, MHSc, FRCPC
Sunnybrook Health Sciences Centre,
2075 Bayview Avenue, Room T2 036, Toronto, ON, M4N 3M5
Tel: (416) 480-4270; *Fax:* (416) 480-6002; *Email:* scott.berry@sunnybrook.ca

Authors

Scott Berry, MD, FRCPC
Sunnybrook-Odette Cancer Centre,
Toronto, Ontario

Calvin Law, MD, MPH, FRCSC
Sunnybrook Health Sciences Centre,
Toronto, Ontario

Contributing Authors

Advisory Board Members/Participants:
Those marked with an * presented evidence for basis of consensus at the meeting.

Dr. Te Vuong
Dr. Jeremy Squire
Dr. Eric Chen*
Dr. Christine Cripps*
Dr. Jean Maroun
Dr.Pierre Major
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Dr. Shun Wong
Dr. Jean-Luc Urbain*
John Kachura*
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Dr. Celia Marginean
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Dr. Andrea McCart
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Dr. Carmen Giacomantonio
Dr. Sender Lieberman
Esther Green RN
Margaret Fitch RN, PhD

Host

Barry D. Stein, BComm, BCL, LLB
President, Colorectal Cancer Association of Canada

ABSTRACT

The purpose of the meeting was to develop a set of national evidence-based standards for assessing and managing patients with metastatic colorectal cancer (mCRC). This report represents the consensus of the multidisciplinary group of Canadian colorectal cancer experts who attended this meeting.

KEY WORDS

Metastatic or advanced colorectal cancer, consensus statement, curative intent metastectomy, liver and lung metastases, multidisciplinary colorectal cancer team and approach, colorectal cancer surgical candidate, targeted systemic agents, chemotherapy standards of care

TERMS OF REFERENCE

Purpose

The purpose of the meeting reported here was to develop a set of national evidence-based standards for assessing and managing patients with metastatic colorectal cancer (mCRC). This report represents the consensus of the multidisciplinary group of Canadian colorectal cancer experts attending this meeting.

Participants

A representative group of Canadian colorectal cancer experts from the key disciplines (surgical, medical and radiation oncology, radiology, interventional radiology, pathology, supportive care) involved in managing mCRC were invited.

Conference sponsors

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APPLICATION OF RECOMMENDATIONS

These standards provide a basis for discussion with patients regarding management options for their mCRC and informed decision-making by patients regarding their care. Individual treatment plans will depend on a complete discussion of the risks and benefits of proposed therapies with individual patients.

Significant progress has been made in improving outcomes for patients with advanced colorectal cancer. The potential for cure through the appropriate use of surgery and systemic therapies should be a primary consideration for all mCRC patients. See **Table 1** for this group's criteria for patients with resectable or potentially resectable metastases and those patients not suitable for metastectomy.

A thorough initial assessment of each patient with mCRC should focus on whether the patient is potentially curable (i.e. may have all their metastatic disease completely resected) or have disease that is unlikely to be cured, either because of the extent and location of disease or the ability of the patient to tolerate the necessary treatment modalities to effect a cure. For those patients who are potentially curable, the initial assessment should address whether it is more appropriate to proceed directly to surgery, or whether the initial use of systemic therapies will ultimately provide the best opportunity to resect all metastases. While improving cure rates and overall survival are important goals, they always need to be tempered by efforts to minimize toxicity with any given treatment choice.

TABLE 1. Metastatic CRC: candidacy for metastectomy

Initially resectable	Potentially resectable	Unresectable
Limited solid metastases (liver or lung) No vital structures impeding resection Good function of predicted residual liver segments No significant comorbid disease	Not deemed initially resectable, but may become surgical candidates with response to localized and/or systemic intervention	Unresectable, widespread disease that will remain unresectable even with good response to systemic therapy

TABLE 2. Relevant multidisciplinary team members involved in mCRC individualized case management

Medical oncology team (MD, RN, pharmacist)
Hepatobiliary surgical team (MD, RN)
Radiologist and interventional radiologist
Radiation oncology team (MD, RN, physicist, radiation therapist)
Oncology pathologist
Social worker and psychosocial support team
Dietitian

Optimally, the assessment of patients with advanced CRC should involve a collaborative, multidisciplinary team (including all relevant medical specialties and allied health professionals — see **Table 2**) and, where possible, review of cases at a multidisciplinary case conference.

All Canadian patients with mCRC should have access to government-funded systemic therapies (and the predictive biomarker testing required to make systemic therapy decisions) that will improve their cure rate when used with surgery, or improve their survival and/or quality of life when used for unresectable metastatic disease.

Although there have been significant advances in the treatment of mCRC in the last decade, further improvements are necessary. Offering patients the option of participating in clinical trials should be a priority, and there should be a continued effort to design and accrue to trials that assess important patient-related outcomes such as quality of life and symptom control in addition to progression-free and overall survival.

QUESTIONS AND CONSENSUS STATEMENTS

THE SURGICAL CANDIDATE

What are the optimal assessment parameters for the curative surgical metastectomy candidate?

All patients with mCRC should be evaluated within a full multidisciplinary team as outlined in **Table 2**, or at least by a minimum of appropriate coordinated surgical, medical imaging, medical oncology and pathology expertise.

The patient's general medical and psychosocial condition, goals and expectations will always be assessed and considered in determining the optimal treatment approaches. The presurgical workup should be holistic in approach. Patients should be stratified into very good surgical risk and moderate surgical risk, including the full extent of metastatic disease. Evaluation of metastatic disease should include assessment of technical factors of resectability, including number and location of metastases, proximity to vital structures and adequacy of residual liver/lung function post resection.

What is the optimal diagnostic assessment for a potentially curable mCRC patient with distant solid metastases?

Diagnostic imaging to determine full extent of disease is the backbone of assessment for a surgical candidate. Mini-

mum sites that should be valued include the thorax, abdomen and pelvis. The rational use of the necessary imaging modalities (computed tomography [CT], positron emission tomography [PET]-CT, magnetic resonance imaging [MRI] and ultrasound) should be planned appropriately, with the appropriate use of multiphasic imaging or the use of specialized contrast agents. In addition, the use of multiple, correlative imaging modalities is recommended to ensure that all metastatic disease has been adequately targeted for therapeutic decision-making. This is specifically important for situations in which nonspecific lesions are described on one imaging modality.

Diagnostic studies for a mCRC patient should be interpreted by an experienced medical imager in oncology, most optimally within the setting of a multidisciplinary clinical interaction or tumour board meeting.

Evaluation of metastatic disease should include assessment of technical factors of resectability, including: number and location of metastases, proximal vital structures, and adequacy of residual liver/lung function post resection.

In addition to the imaging studies, within a year of the onset of metastatic disease, patients being considered for metastectomy should have an endoscopic evaluation, specifically a colonoscopy, to evaluate recurrent or synchronous or metachronous disease.

Who is considered the optimal metastectomy candidate?

The goal of metastectomy is to have an R0 resection of all metastatic disease. The primary tumour must have been completely resected or is potentially resectable.

Optimally resectable patients with hepatic mCRC have a favourable combination of patient factors, technical resection factors and biologic behaviour. Patient characteristics include adequate medical status and no history of or risk factor for hepatic compromise. Technical characteristics include: 1) two or more contiguous liver segments of adequate function without metastases; 2) noninvolvement of one portal vein and one ipsilateral hepatic vein; 3) no compromise of the biliary hilum; and 4) smaller (≤5cm) maximal size of the largest metastatic lesion. Finally, favourable biologic behaviour includes: 1) metachronous lesion; 2) primary lesion with low risk of local recurrence; 3) low primary nodal burden of disease (<N2).

What is the optimal timing of primary resection and metastectomy for the patient with mCRC?

The timing of primary resection in the face of synchronous mCRC should be part of the multidisciplinary team/multidisciplinary case conference discussion.

The timing of metastectomy is critical and there are some patients who are optimal candidates for immediate surgery (e.g. single lung/liver metastases).

Preoperative systemic therapy could be considered. Given the potential hepatotoxicity of preoperative chemotherapy, the appropriate selection of patients with liver metastases is important. Should preoperative systemic therapy be utilized, the neoadjuvant period of treatment should not exceed 6–9 cycles (given every 2 weeks), and metastectomy should take place within 4–8 weeks following any systemic therapy, to minimize toxicity while avoiding progression.

There may be some patients, possibly identified by clinical risk evaluation demonstrating optimal response to surgical resection (**Table 3**), in whom proceeding directly to surgical resection is the optimal decision. For patients proceeding directly to surgical resection of metastases, it is recommended that surgery take place as soon as possible.

What is the role of systemic therapy for patients with resectable mCRC?

Patients with resectable liver metastases should receive systemic therapy either peri- or postoperatively (EPOC[1] and Mitry[4]). The optimal method of delivering systemic therapy in this situation is not known and is being assessed in the NSABP C-11 trial (perioperative vs postoperative 5FU + leucovorin + oxaliplatin [FOLFOX] in patients with resectable liver metastases). However, given the potential hepatotoxicity of preoperative chemotherapy, the appropriate selection of patients with liver metastases is important to determine those who may not require preoperative systemic therapy (**Table 3**).

Coordination of perioperative systemic therapy and surgery requires close collaboration between medical and surgical oncologists, to ensure surgery and systemic therapy occur in a coordinated and timely fashion in relation to each other.

TABLE 3. Ideal candidates for immediate metastectomy or preoperative systemic therapy

Candidate for immediate metastectomy	Candidate for preoperative systemic therapy and then metastectomy
• Low number of metastases (e.g. single vs multiple) • Low volume/size of metastases (e.g. <5cm) • 2 or more contiguous segments of adequate hepatic function without metastatic involvement • No involvement in the biliary hilum • No involvement of 1 portal vein and 1 ipsilateral hepatic vein • Metachronous disease • Otherwise favourable prognosis with low risk of further systemic recurrence • Health history indicates concern for potentially augmented hepatotoxicity from preoperative systemic therapy (i.e. pre-existing steatosis)	• Liver function within normal limits • Less favourable prognosis for further local or systemic recurrence (i.e. N2 primary disease or close margin primary resection) • Concern for inability to perform R0 metastectomy due to the number, size or location of metastases

What is the role of surveillance for the postmetastectomy patient?

Although there is no randomized evidence, it is reasonable that all patients following metastectomy should have ongoing surveillance that should be consistent with the guidelines for followup for Stage II and III patients post-tumour resection (i.e. initially imaging and carcinoembryonic antigen [CEA] every 3–6 months). Additional diagnostic imaging followup should be inclusive of the site of metastectomy.

Consensus statements pertaining to the surgical candidate have taken account of: Nordlinger et al 2009,[1] Van Cutsem et al 2010,[2] Power et al 2010,[3] Mitry et al 2008 ,[4] Vickers et al 2010,[5] Kopetz et al 2009[6]

MANAGEMENT OF THE PATIENT WITH POTENTIALLY RESECTABLE METASTASES

What is the role and type of systemic therapy for the potential surgical mCRC candidate?

The objective of therapy for this group of patients is to render the metastases resectable. Unlike the patients who have initially resectable metastases, where there are randomized clinical trials showing progression-free survival improvements with the use of systemic therapy, similar evidence does not exist for the borderline surgical candidate. There is one randomized Phase II trial done in this group of patients (CELIM trial[7]) but patients in both arms of this trial received biologic therapies, and there are no randomized comparisons of chemotherapy with or without biologics. Until randomized evidence is available, a rational approach could be to select the systemic therapy that will maximize response given the retrospective data that demonstrates a correlation of tumour response rate with R0 resection rate in this group of patients (Folprecht[8]).

Nonsurgical ablative therapies (radiofrequency ablation [RFA], microwave etc.) and interventional radiology strategies (e.g. portal vein embolization [PVE]) should be considered, where appropriate, to achieve potential resectability. Given the risk of liver toxicity from cumulative chemotherapy, patients should be assessed at 8–12-week intervals after the start of systemic therapy, to assess resectability on a regular basis. Metastectomy should occur as soon as the metastases are deemed resectable.

For patients whose metastases are rendered resectable with systemic therapy, it would be reasonable to consider postoperative systemic therapy.

For the patient whose metastases do not become resectable, the patient should follow the systemic therapy guidelines as outlined in the section *Management of the Nonsurgical Patient.*

What is the optimal management of the primary tumour and surgical approach in the face of symptomatic vs asymptomatic disease?

For patients with a symptomatic primary that is not amenable to treatment with systemic or radiation therapy, surgical resection of that primary, which may result in optimal palliation, should be considered.

Otherwise, an asymptomatic primary should be considered for resection in relation to the resectability of the synchronous metastatic disease.

For patients whose metastases become resectable, the timing of resection of the primary for those with synchronous metastases should be part of the multidisciplinary team/multidisciplinary case conference discussion.

If metastases remain unresectable, the primary tumour should be managed with the most appropriate palliative modality(ies) as determined through a multidisciplinary tumour board.

Consensus statements pertaining to the management of the patient with potentially resectable metastases have taken account of: Folprecht et al 2010,[7] Van Cutsem et al 2010[2], Power et al 2010,[3] Vickers et al 2010,[5] Folprecht et al 2005,[8] Poultsides et al 2009[9]

MANAGEMENT OF THE NONSURGICAL PATIENT

The recommendations in this section apply to patients with mCRC who, after a rigorous multidisciplinary assessment, are not considered candidates for potentially curative surgery. This assessment will be made in situations where the patient will not be able to tolerate surgery or, because of the extent of metastatic disease, would not be able to undergo complete surgical resection even with optimal response to systemic therapy.

Notwithstanding the initial assessment, reevaluation of any patient's resectability should they have an excellent response to systemic therapy is appropriate, giving due consideration to potential hepatotoxicity from the systemic therapy they have received.

What is the optimal sequencing of chemotherapy with/without biologic therapies?

Treatment algorithms are outlined in **Figure 1** (for patients with KRAS wild-type tumours) and **Figure 2** (for KRAS mutant tumours). If the combination of chemotherapy and epidermal growth factor receptor (EGFR) inhibitor is selected as a first-line treatment option, the combinations of capecitabine, oxaliplatin and cetuximab (COIN trial[25]) or Nordic 5FU + leucovorin + oxaliplatin (FLOX) and cetuximab (NORDIC VII)[26] should not be used, given their lack of efficacy compared with chemotherapy alone.

For selected patients, a sequential approach starting with fluoropyrimidine monotherapy is appropriate, given randomized trials demonstrating similar benefits of this approach to the initial use of chemotherapy doublets[13,32]. Policymakers should fund agents to permit this type of sequential therapy.

Triplet combination therapy (i.e. FOLFOX + irinotecan [FOLFOXIRI] Falcone[27]) has demonstrated a survival benefit compared to irinotecan and infusional 5FU and could also be considered as an initial systemic therapy for these patients; however, it has not yet been compared head-to-head against doublet chemotherapy and a biologic.

FIGURE 1. Systemic therapy for the nonsurgical patient who is KRAS wild-type

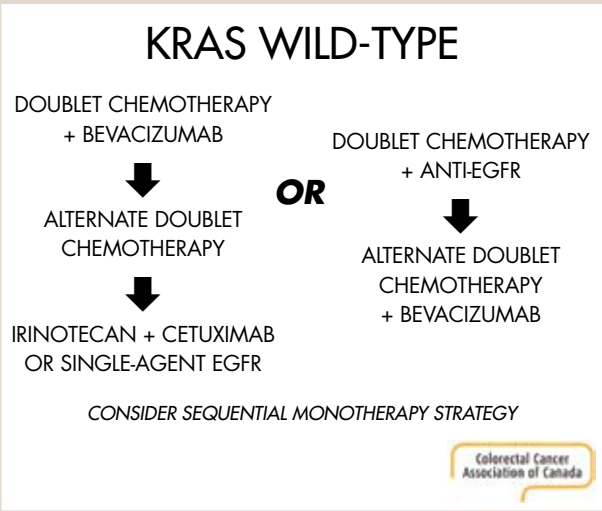

FIGURE 2. Systemic therapy for the nonsurgical patient who is KRAS mutant

What is the optimal use of systemic therapy with radiation or radiofrequency ablation for the mCRC patient who is a nonsurgical candidate?

The use of nonsurgical ablative (e.g. stereotactic body radiation therapy [SBRT] or RFA) techniques should be considered as part of the multidisciplinary discussion regarding the care of these patients.

Consensus statements pertaining to the management of the nonsurgical patient have taken account of:
Rothenberg et al 2008,[10] Van Cutsem et al 2004,[11] Koopman et al 2007,[12] Tournigand et al 2004,[13] Fuchs et al 2007,[14] Hurwitz et al 2004,[15] Saltz et al 2008,[16] Cassidy et al 2008,[17] Bokemeyer et al 2007,[18] Jonker et al 2007,[19] Sobrero et al 2008,[20] Van Cutsem et al 2009,[21] Douillard et al 2010,[22] Kohne et al 2008,[23] Amado et al 2008,[24] Maughan et al 2010,[25] Tveit et al 2011,[26] Falcone et al 2007,[27] Karapetis et al 2008,[28] Cunningham et al 2004,[29] Giantonio et al 2007,[30] Peeters et al 2010,[31] Seymour et al 2007,[32] Van Cutsem 2009[33]

What is the role of biomarker testing in mCRC?

Assessment of the patient's tumours' KRAS mutation status as soon as possible after the diagnosis of metastases is critical, given the importance of this biomarker in selecting optimal treatment options. Other appropriate biomarkers (e.g. BRAF providing prognostic information) could be considered.

Sufficient numbers of accredited centres with established quality assurance standards should exist to ensure timely access to the appropriate biomarkers necessary for informed discussions between patients and their oncologists.

This consensus statement has taken account of:
Allegra et al 2009[34]

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Conflicts of interest

Participants disclosed potential conflicts of interest with the past 2 years:
- Scott Berry: Sanofi-Aventis, Roche, Amgen, Bristol-Meyers-Squibb
- Calvin Law: Sanofi-Aventis, Roche, Amgen, Bristol-Meyers-Squibb

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