



Improving the care of colorectal cancer patients

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Corresponding Author: Sheryl Koski, MD, FRCPC, MHPE

Cross Cancer Institute, 11560 University Avenue, Edmonton, AB T6G 1Z2;

Tel: (780) 432-8682; Fax: (780) 432-8888; Email: sherylko@cancerboard.ab.ca

Authors:

Sheryl Koski, MD, FRCPC

Cross Cancer Institute, Edmonton, Alberta

Shahid Ahmed, MD, FRCPC

Saskatchewan Cancer Agency, Saskatoon, Saskatchewan

Diane Severin, MD, FRCPC

Cross Cancer Institute, Edmonton, Alberta

John Yee, MD, FRCSC

Vancouver General Hospital, Vancouver, British Columbia

Ralph Wong, MD, FRCPC

Manitoba Cancer Agency, Winnipeg, Manitoba

Sharlene Gill, MD, MPH, FACP, FRCPC

BC Cancer Agency, Vancouver, British Columbia

Contributing authors

Dr. Helen Anderson, Dr. Heather-Jane Au, Dr. Ardashes Avanesian, Dr. Oliver Bathe, Dr. Malcolm Brigden, Dr. Neil Chua, Dr. Paul Daeninck, Dr. Scot Dowden, Dr. Jacob Easaw, Dr. Tony Fields, Dr. Jiti Gill, Dr. Joel Gingerich, Dr. Vallerie Gordon, Dr. Kamal Haider, Dr. Edward Hardy, Dr. Hamish Hwang, Dr. Kurian Joseph, Dr. Karen King, Dr. Marianne Krahn, Dr. Steven Latosinsky, Dr. Lyly Le, Dr. Pamela Leco, Dr. Howard Lim, Dr. D. Ross McLean, Dr. Barbara Melosky, Dr. Karen Mulder, Dr. Tirath Nijjar, Dr. Gregory Polyakov, Dr. Ewan Robson, Dr. Amer Sami, Dr. Michael Sawyer, Dr. Andrew Scarfe, Dr. Daniel Schiller, Dr. Diane Severin, Dr. Claudia Strehlke, Dr. Nawaid Usmani, Dr. Nobby Woo, Dr. Sunil Yadav, Dr. Brent Zabolotny

TERMS OF REFERENCE

Purpose

- This is a consensus opinion of oncologists and allied health professionals from across Western Canada intended to define best care practices and improve best care and outcomes for patients with colorectal cancer (CRC).

Participants

- Medical, radiation and surgical oncologists and allied health professionals involved in the care of patients with CRC.

Target audience

- Healthcare professionals involved in the care of CRC patients.

Basis of recommendations

- The recommendations provided are on the basis of best available evidence. A brief summary of each topic with applicable references is included.

HISTORY OF THE WCS

The Western Canadian Colorectal Cancer Consensus Conference (WC5) was initiated in 1999, in Edmonton, Alberta, by Dr. A.L.A. Fields. The WC5 is an interactive, multidisciplinary conference attended by oncologists and allied health professionals from across Western Canada involved in the care of CRC patients. It is a forum to facilitate the discussion of evidence among these healthcare professionals. The goal is to develop evidence-based consensus recommendations on key emerging issues that relate to improvements in best care practices and outcomes for CRC patients throughout Western Canada. Through this forum, participating provinces have been able to move forward with important advances in the management of CRC.

Examples of practice changes that have emerged from this meeting include the use of combination chemotherapy in the treatment of metastatic CRC (1999, Edmonton), the change from bolus to infusional fluorouracil combination regimens in the treatment of metastatic CRC (2000, Vancouver), the introduction of FOLFOX chemotherapy as adjuvant treatment of CRC (2004, Saskatoon) and the use of biologic agents in the treatment of metastatic CRC (2007, Winnipeg).

Conference sponsors

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MSI STATUS

Question: Should microsatellite instability status be used as a factor in predicting patient suitability for adjuvant chemotherapy?

Consensus statement

- Microsatellite instability testing should be available to aid in decision making for patients with Stage II colon cancer who are being considered for fluoropyrimidine monotherapy (Level II-2).

Summary of evidence

Microsatellite instability (MSI) is an indicator of deficient mismatch repair (MMR) reflecting an underlying defect in the DNA mismatch repair gene system, which is responsible for correction of errors arising during cell division. These base deletions or insertions occur primarily due to inactivation of one or more of the dominant mismatch repair genes: MLH1, MSH2, MSH6 and PMS2. Approximately 15% of sporadic colorectal cancers are characterized by MSI, mostly due to epigenetic hypermethylation of MLH1. The role of MSI as a prognostic and predictive marker in CRC has been a topic of intense interest over recent years.

It was postulated that defects in DNA mismatch repair may confer tolerance to acquired DNA damage. In in-vitro cell models of MSI, deficient MMR (dMMR) systems were insensitive to fluorouracil, while cells proficient in MMR (pMMR) were capable of recognizing fluorouracil incorporation into DNA, resulting in cell-cycle checkpoint arrest.¹ In 2003, Ribic et al reported an analysis of 570 tumour specimens from patients with Stage II or III colon cancer enrolled in randomized trials of adjuvant fluorouracil chemotherapy. Among the 16.7% with high-frequency microsatellite instability (MSI-H), adjuvant chemotherapy did not correlate with survival benefit.² Carethers et al made a similar observation in a smaller study using patient data and tumour samples from a US Veterans' hospital registry.³ However, an analysis of patients from 4 randomized adjuvant therapy trials from the National Surgical Adjuvant Breast and Bowel Project failed to confirm the negative predictive value of MSI-H.⁴

At the American Society of Clinical Oncology 2008 Annual Meeting, Sargent et al presented a pooled analysis of data from 5 randomized trials. Testing was done for MMR status by immunohistochemistry on the tumours of 491 patients with Stage II or III colon cancer who had received fluorouracil-based adjuvant chemotherapy or no chemotherapy. In this analysis, 49% of patients had Stage II disease and 15% were dMMR. Five-year disease-free survival (DFS) was not significantly different between treated vs untreated patients in those with dMMR Stage II colon cancer, pMMR Stage II colon cancer and dMMR Stage III colon cancer. As expected, the 5-year DFS was superior in treated patients with pMMR Stage III disease (DFS 61% treated vs 41% untreated; $p = 0.003$).⁵ The results in the Stage II patients were pooled with those from a previous study by the same research group, which yielded 1027 patients, of whom 16% were dMMR.² In this pooled set, the 5-year DFS was higher

in the untreated vs treated Stage II dMMR patients (87% untreated vs 72% treated; $p = 0.05$), as was the 5-year overall survival (93% untreated vs 75% treated; $p = 0.03$).⁵ This was the largest analysis of its kind to date: it further verified the lack of benefit from adjuvant fluorouracil treatment in patients with MSI-H colon cancers and suggested a decrease in survival in the subset of patients with Stage II disease.

The decision to offer patients adjuvant chemotherapy for Stage II colon cancer is based on a number of patient and tumour characteristics which retrospective data show are associated with poorer outcomes. The presence of MSI identifies a subset of patients who may not benefit from fluoropyrimidine monotherapy; therefore MSI testing should be made available to aid in the decision-making process. How this will impact the treatment decision in the presence of other adverse prognostic factors is at the discretion of the treating oncologist. Current data do not allow conclusions to be made about the impact of MSI status in the context of oxaliplatin-based adjuvant regimens.

DIET AND EXERCISE

Question: Should recommendations for diet and exercise be included as standard followup for patients with CRC?

Consensus statement

- Recommendations should be made as part of standard followup for all patients with CRC (Level II-2).
- Recommendations for diet should be in accordance with Canada's Food Guide.⁶ Recommendations for exercise should be in accordance with Canada's Physical Activity Guide to Healthy, Active Living (Level II-2).⁷

Summary of evidence

Although existing evidence regarding the impact of dietary intervention and physical activity in CRC is primarily observational, retrospective and in the primary prevention setting, compelling data suggest that diet and exercise are associated with risk of recurrence and development of new CRC after definitive treatment of localized CRC. Increased fibre intake and decreased red and processed meat intake have been associated with decreased incidence of CRC.^{8,9} In an analysis of randomized subjects in the CALGB 89803 adjuvant Stage III colon cancer trial of irinotecan + fluorouracil + leucovorin vs fluorouracil + leucovorin, a "Western" dietary pattern (higher intake of red and processed meats, sweets, french fries and refined grains) was associated with inferior DFS (HR 3.25; 95% CI 2.04 to 5.19).¹⁰ Multiple studies have also demonstrated an association between vitamin D use and lower risk of CRC recurrence.¹¹ It is postulated that binding of vitamin D receptors expressed in colon cancer cells by circulating 1,25-hydroxyvitamin D leads to protective effects of apoptosis induction, inhibition of proliferation and anti-angiogenic effects. In a prospective, nested observational study, higher prediagnosis plasma 1,25-hydroxyvitamin D levels were associated with a significant reduction in overall mortality.¹²

Physical activity is believed to be associated with a reduced incidence of CRC by reduction of hyperinsulinemia and downregulation of insulin growth factor-1 (IGF1)-related oncogenic pathways. Data from several studies have suggested a protective effect of increased exercise. Notably, in a prospective observational Nurses Health Study analysis of 573 women diagnosed with Stages I to III CRC, the risk of CRC-specific mortality was 0.39 (95% CI 0.18 to 0.82) for women exercising greater than 18 metabolic equivalent (MET)-hours per week compared with women exercising less than 3 MET-hours/week.¹³ An exercise subanalysis of CALGB 89803 yielded similar findings with a 43% improvement in 3-year DFS (75.1% vs 84.5%) for women exercising more than 18 MET-hours/week.¹⁴ The strength of this observational evidence is the rationale supporting the upcoming NCIC.CO21 Phase III study of the impact of a physical activity program on DFS in patients with high-risk Stage II or Stage III colon cancer (CHALLENGE).

In view of the supporting evidence, albeit largely observational and retrospective, and given the general health benefits of a balanced diet and increased physical activity, it is agreed that recommendations supporting dietary guidelines as set forth by the Canada Food Guide⁶ and Canada's Physical Activity Guide to Healthy, Active Living⁷ should be included in the guidance provided to patients after definitive treatment of Stage I to III CRC. In addition, efforts to generate Level I evidence and support accrual to NCIC.CO21 are encouraged.

Levels of evidence

Several different systems are in use for rating levels of evidence,⁴² with slight variations among them. This report uses the one developed by the Canadian Task Force on Preventive Health Care (available at www.ctfphc.org > History & Methods. Table 2. Levels of Evidence — Research Design Rating):

- I Evidence from randomized controlled trial(s)
- II-1 Evidence from controlled trial(s) without randomization
- II-2 Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group
- II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
- III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

NEOADJUVANT THERAPY FOR RECTAL CANCER

Question: What are the criteria for the choice of neoadjuvant therapy for rectal cancer?

Consensus statement

- Any of the following are criteria for long-course chemoradiation therapy as neoadjuvant therapy for rectal cancer (Level I):
 1. When the tumour is invading other structures, is tethered or is fixed
 2. When the circumferential margin is likely to be positive (< 2 mm)
 3. Low-lying tumours (< 5 cm)
 4. Other situations where the surgeon feels downstaging may assist with resectability
- The criterion for short-course radiation therapy is T3 tumours felt to be resectable without any of the above features (Level I).
- Nodal status cannot be reliably assessed preoperatively and does not drive the decision for neoadjuvant treatment (Level II-2).

Summary of evidence

Preoperative short-course radiotherapy and long-course chemoradiotherapy both offer improvements in local control. In the total mesorectal excision (TME) era, local recurrence rates have varied between 4.7% and 10.6% with the use of adjuvant short-course or long-course radiotherapy.¹⁵⁻¹⁹ Downstaging from long-course preoperative chemoradiotherapy can help to improve sphincter preservation.²⁰

Circumferential resection margin positivity increases the rate of local recurrences.^{21,22} Avoidance of a positive margin is therefore critical. If there is a surgical risk of margin positivity, as in tethered or fixed tumours, long-course chemoradiotherapy is recommended. Very low-lying tumours can sometimes be difficult to resect with clear margins and if these are staged as T3, consideration should be given to long-course chemoradiotherapy. Tumours that are mobile, in the mid to upper rectum and felt to be resectable with clear margins can be treated with preoperative short-course radiotherapy.

Toxicity of short-course radiotherapy has been well documented in the Dutch TME trial.²³ The toxicity of long-course chemoradiotherapy has not been reported in such detail, other than in the trial by Bujko et al which reported similar rates of toxicity with long- and short-course treatments.²⁴ Based on the evidence, it cannot be presumed that short-course therapy is more toxic than long-course chemoradiotherapy.

KRAS TESTING

Question: Is testing for KRAS status necessary to develop therapeutic strategies for CRC patients?

Consensus statement

- KRAS testing is necessary in patients who are being con-

sidered for anti-EGFR monoclonal antibody therapy. Patients with mutant KRAS tumours are not candidates for anti-EGFR monoclonal antibody therapy (Level I).

Summary of evidence

The efficacy of the monoclonal antibodies (mAbs) cetuximab and panitumumab, targeting epidermal growth factor receptor (EGFR) — alone or in combination with cytotoxic agents — has been demonstrated in both chemotherapy-refractory and untreated metastatic CRC (mCRC).²⁵⁻²⁸ Nevertheless, only a subgroup of patients with mCRC derives benefit from EGFR inhibitors. Several clinicopathologic factors have been proposed to predict response to anti-EGFR mAbs. Among those predictive factors, KRAS gene mutational status has emerged as a robust biomarker. Approximately 30% to 40% of CRCs harbour a mutation in the KRAS gene. Several randomized trials have demonstrated that EGFR-independent, constitutive activation of the KRAS signalling pathway could impair the response to anti-EGFR mAbs.

In the NCIC CO.17 trial, the benefit of cetuximab monotherapy in pretreated mCRC was confined to patients with wild-type KRAS tumours. In such patients, cetuximab monotherapy was associated with an almost doubling of median overall survival (OS) and progression-free survival (PFS) over best supportive care (BSC), with median PFS of 3.8 vs 1.9 months (HR 0.40; $p < 0.001$) and median OS of 9.5 vs 4.8 months (HR 0.55; $p < 0.0001$).²⁹ Patients with mutant KRAS tumours had median PFS of 1.8 months with or without cetuximab treatment. Similarly, panitumumab monotherapy in chemotherapy-refractory patients was beneficial only in patients with wild-type KRAS tumours with a median PFS of 12.3 vs 7.3 weeks with BSC only ($p < 0.0001$).³⁰ No benefit was derived with panitumumab monotherapy in patients with KRAS mutant tumours (median PFS 7.4 vs 7.3 weeks; $p = \text{NS}$). Similar results were obtained in trials where anti-EGFR mAbs were used in combination with chemotherapy in previously untreated patients. For example in the CRYSTAL trial, in patients with KRAS wild-type tumours addition of cetuximab to FOLFIRI improved response rate and PFS over FOLFIRI alone, with response rates of 59% vs 43% ($p = 0.002$) and median PFS of 9.9 vs 8.7 months (HR 0.68; $p = .017$).³¹ In the OPUS trial, which evaluated the effect of cetuximab in combination with FOLFOX, addition of cetuximab to FOLFOX produced significant improvements in response rate (61% vs 37%; $p = 0.01$) and PFS (7.7 vs 7.2 months; $p = 0.02$) in patients with wild-type KRAS tumours.³² The addition of cetuximab to FOLFOX in patients with KRAS mutant tumours was associated with a shorter PFS of 5.5 vs 8.6 months (HR 1.83; $p = 0.02$). Likewise, in the CAIRO-2 trial the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab in patients with KRAS-mutated tumours had a detrimental effect, with median PFS of 8.6 vs 12.5 months ($p = 0.043$).³³

In conclusion, randomized trials evaluating KRAS gene mutational status in more than 2000 patients with mCRC have shown that the benefit of EGFR-targeted monoclonal antibodies is confined to patients with wild-type KRAS tumours.²⁷⁻³¹ KRAS mutations predict for lack of clinical

benefit of cetuximab or panitumumab therapy. This effect is seen with both cetuximab and panitumumab, with regimens containing oxaliplatin or irinotecan and with first-line and other lines of therapy. These findings support routine KRAS testing of patients with mCRC being considered for treatment using EGFR-based antibodies. Patients with a known KRAS mutation should not be treated with cetuximab or panitumumab.

SURGERY FOR LUNG METASTASES

Question: Which patients are candidates for lung metastasectomy?

Consensus statement

- A patient with advanced CRC with all the following features should be considered for lung metastasectomy (Level III):
 1. Potentially resectable metastases (in their entirety)
 2. Primary disease is controlled
 3. No extrathoracic metastases, with the exception of resectable liver metastases
 4. Good surgical candidate with adequate pulmonary reserve


Summary of evidence

Approximately 10% of patients with lung metastases present with potentially resectable disease. Evidence on the optimal management of these patients is limited. No randomized controlled trials exist, and much of practice is based on extrapolation from studies of liver metastasectomy. Median survival in the range of 40% to 60% at 5 years has been consistently reported after pulmonary metastasectomy. Five-year survival approaching 50% can be achieved with complete resection, even with a prior history of pulmonary or hepatic metastasectomy. Although the surgical literature is limited to retrospective case series, elevated carcinoembryonic antigen (CEA) level and increased number of pulmonary metastases have been found to be predictors of poor prognosis after pulmonary resection.³⁴ Age, sex, primary tumour stage, preoperative CEA, disease-free interval, and prior hepatic metastasectomy were not found to influence survival in patients undergoing repeat pulmonary resection.³⁵ Lymph node involvement appears to strongly influence prognosis. Veronesi et al described 46% 5-year survival after pulmonary metastasectomy, as compared to 17% and 0% when hilar or mediastinal nodes, respectively, were histologically positive. Twenty percent of patients had lymph node involvement and many were unexpectedly found to be positive only at the time of surgery.³⁶ Welter et al also found that lymph node involvement predicted very poor prognosis.³⁷ Patients with multiple pulmonary metastases are more likely to have lymph node involvement, and lymph node sampling is therefore recommended.³⁸

In a recent review, Pfannschmidt et al analyzed 20 studies involving 1870 patients. Seventeen studies, which included 1684 patients, were of lung metastasectomy alone. The median 5-year survival was 48% (range 41.1% to 56%).

Normal preoperative CEA was associated with 59.3% median 5-year survival as compared to only 18.9% when CEA was elevated, but this was not a consistent finding. The influence of a short disease-free interval (between colon resection and the appearance of pulmonary metastases) on prognosis after pulmonary resection is not clear based on available data. Patients with a short disease-free interval or elevated CEA should not be excluded from consideration for pulmonary metastasectomy if a R0 resection is deemed possible.³⁹

Pulmonary metastasectomy may also be considered for patients with metachronous or synchronous liver and lung metastases. Pfannschmidt et al's review included 3 studies with 186 patients who underwent lung and liver metastasectomy. The median survival for this group of patients was 31% (range 30% to 38%).³⁹ Joosten et al reported no difference in median DFS, 2-year-survival or 5-year survival following resection in patients presenting with lung and liver metastases as compared to those presenting with only lung metastases.⁴⁰ Although metachronous pulmonary metastases after hepatic resection are more common, Shah et al found no difference in overall survival for patients with synchronous vs metachronous presentation of lung and liver metastases. Staged resection was shown to be safe, and an aggressive multidisciplinary surgical approach was advocated.⁴¹

In summary, available evidence does support a role for resection of lung metastases from CRC in a select group of patients who are fit for surgical intervention. The metastatic disease should be resectable in its entirety and there should be no evidence of extrathoracic disease, with the exception of resectable liver metastases. Patients in whom resectable disease recurs should be considered for further surgical resection. 

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Disclosures

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