Eastern Canadian Colorectal Cancer Consensus Conference 2017

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Published

2018

Journal Title

Current Oncology

Version

Version of Record (VoR)

DOI

10.3747/co.25.4083

CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

Eastern Canadian Colorectal Cancer Consensus Conference 2017

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ABSTRACT

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference 2017 was held in St. John's, Newfoundland and Labrador, 28–30 September. Experts in radiation oncology, medical oncology, surgical oncology, and cancer genetics who are involved in the management of patients with gastrointestinal malignancies participated in presentations and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses multiple topics in the management of gastric, rectal, and colon cancer, including

- identification and management of hereditary gastric and colorectal cancer (CRC);
- palliative systemic therapy for metastatic gastric cancer;
- optimum duration of preoperative radiation in rectal cancer—that is, short- compared with long-course radiation;
- management options for peritoneal carcinomatosis in CRC;
- implications of tumour location for treatment and prognosis in CRC; and
- new molecular markers in CRC.

Key Words Guidelines, gastric cancer, colorectal cancer, rectal cancer, peritoneal carcinomatosis, chemotherapy, radiation therapy, immunotherapy, molecular markers, hereditary cancer syndromes

Curr Oncol. 2018 Aug;25(4):262-274 www.current-oncology.com

INTRODUCTION

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference 2017 was held in St. John's, Newfoundland and Labrador, 28–30 September. The purpose of the conference was to develop consensus statements on emerging and evolving concepts.

Participants were Canadian medical oncologists, radiation oncologists, surgical oncologists, and cancer geneticists from across Ontario, Quebec, and the Atlantic provinces. The recommendations proposed here represent the consensus opinion of health care professionals involved in the care of patients with gastrointestinal malignancies.

Basis of Recommendations

The existing scientific evidence was presented and discussed at the meeting. Recommendations were formulated within the group and categorized by level of evidence[1] as follows:

- Level I: evidence from randomized controlled trials
- Level II-1: evidence from controlled trials without randomization
- Level II-2: evidence from analytic cohorts or case–control studies, preferably from more than one centre or research group
- Level II-3: evidence from comparisons between times or places with and without the intervention

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(dramatic results in uncontrolled experiments could be included here)
- Level III: Opinion of respected authorities, based on clinical experience; descriptive

GASTRIC CANCER

Question 1

How can we identify patients and families that should be referred for genetic assessment for hereditary gastric cancer, and how should such patients be managed?

- The following situations were recognized as criteria that should trigger a referral for genetic testing for hereditary diffuse gastric cancer (HDGC) [level III unless otherwise stated]:
  - Diagnosis of 1 case of diffuse gastric cancer (DGC) at less than 40 years of age
  - Diagnosis of 2 gastric cancer cases regardless of age, at least 1 confirmed to be DGC
  - Personal or family history of DGC and lobular breast cancer (LBC), 1 diagnosed at less than 50 years of age
  - Bilateral LBC or family history of 2 or more cases of LBC diagnosed at less than 50 years of age
  - *In situ* signet-ring carcinoma or pagetoid spread of signet-ring cells

  Each jurisdiction should, however, take into consideration local patterns.
- Patients with strong family history of gastric cancer who initially test negative for pathogenic mutations may be referred back to genetics every 3–5 years for further testing. Intestinal-type gastric cancer does not warrant testing.
- General recommendations for the management of patients with pathogenic E-cadherin *(CDH1)* mutations consistent with HDGC are as follows [level III unless otherwise stated]:
  - Prophylactic total gastrectomy should be advised for individuals testing positive for pathogenic *CDH1* mutations in early adulthood. Timing should, however, give consideration to the family history of age of onset and childbearing plans.
  - Surgical gastrectomy specimens must be examined using HDGC-specific protocols.
  - For individuals not undergoing prophylactic surgical management, regular endoscopy with random biopsies should be performed annually. However, it is important that patients understand the limitations of screening.
  - Chromoendoscopy is not recommended.
- Finally, the group recommended that consideration be given to the increased risk of gastric cancer with other hereditary cancer syndromes, including Lynch syndrome, familial adenomatous polyposis (FAP), gastric adenocarcinoma, gastric adenocarcinoma and proximal polyposis of the stomach, and Peutz–Jeghers syndrome [level III].

Evidence Summary

Although most gastric cancers are considered sporadic, estimates suggest that 5%–10% have a familial component, and 1%–3% are associated with an inherited cancer predisposition syndrome[2]. One such syndrome is HDGC, which is associated with the development of diffuse (signet-ring cell) gastric cancers at a young age (average: 37 years) attributable to autosomal dominant inheritance of truncating mutations in the cell adhesion protein E-cadherin *(CDH1)*[3]. The lifetime risk of gastric cancer in men and women with confirmed pathogenic mutations in *CDH1* is 40%–70% and 56%–83% respectively. Furthermore, women with pathogenic *CDH1* mutations have a 40%–50% risk of developing invasive LBC[4].

Overall, the group endorsed the recent international expert consensus recommendations published by van der Post *et al.*[3] for the diagnosis and management of HDGC. Those recommendations established these criteria for genetic testing for *CDH1* mutations: 1 case of DGC diagnosed at less than 40 years of age; 2 gastric cancers diagnosed at any age, with at least 1 being DGC; and a personal or family history of DGC and LBC, with 1 case diagnosed at less than 50 years of age. Furthermore, testing for HDGC should be strongly considered if there is a history of bilateral LBC or a family history of 2 or more cases of LBC diagnosed at less than 50 years of age, or pathology showing evidence of either or both of *in situ* signet-ring carcinoma or pagetoid spread of signet-ring cells. Lack of E-cadherin staining by immunohistochemistry (IHC) should also raise suspicions about the possibility of HDGC.

The group again broadly endorsed the van der Post HDGC guidelines relating to the management of patients with confirmed pathogenic *CDH1* mutations[3], including early referral of patients for consideration of prophylactic gastrectomy (regardless of endoscopic findings). Patients who decline prophylaxis should be offered at least annual endoscopy, with random biopsy of defined gastric locations, pale regions, and lesions of concern. However, it is important that patients understand the significant limitations of surveillance. Also highlighted is the importance of surgical gastrectomy specimens being examined using HDGC-specific protocols to ensure that early cancers are not missed.

Other inherited cancer syndromes are associated with variable risks of gastric cancer, which can be as high as 25% for Peutz–Jeghers syndrome and as low as 1% for FAP[2]. The group therefore advises that the risk of hereditary gastric cancer also be considered in patients presenting with a confirmed diagnosis or features suggestive of those hereditary cancer syndromes and others (see Oliveira *et al.*[2] for a review).

Question 2

What are the evidence-based principles of care for patients with metastatic gastric cancer?

- The primary focus of care should always be symptom relief and improved quality of life, with involvement of a multidisciplinary team in treatment planning, which should include early palliative care referral [level III].
- Palliative surgical or endoscopic procedures (or both)—and palliative radiation—should also be considered in symptomatic patients [level III].

- Combination chemotherapy is superior to single-agent treatment for overall survival (OS), if patients are fit [level I].
- Upfront HER2 testing is recommended in gastric and gastroesophageal junction adenocarcinomas in designated centres, because such testing is necessary to select appropriate first-line treatment. However, a delay in the test results should not delay commencement of palliative chemotherapy [level III].
- Established first-line combination chemotherapy regimens (defined in the evidence summary that follows) for HER2-negative or unknown cancers include ECX, ECF, EOX, EOF, CF, CX, FOLFOX, XELOX, FOLFIRI, DCF, modified DCF [level I].
- For HER2-positive gastric adenocarcinomas in which the patient is a candidate for platinum-based chemotherapy, treatment should begin with first-line trastuzumab plus chemotherapy. Prior cardiac evaluation, including echocardiography or multi-gated acquisition imaging should be considered [level I].
- Established first-line combination chemotherapy regimens (defined in the evidence summary that follows) for HER2-positive cancers include HCF and HCX [level I].
- Strong consideration should be given to treatment toxicity profiles and to patient preference and convenience when selecting therapies [level III].
- Compared with best supportive care (BSC), second- and subsequent-line chemotherapy has been associated with improvements in OS and quality of life [level I].
- Ramucirumab is active in the second line in combination with paclitaxel, being associated with improvements in survival and quality of life [level I]. However, given an increased risk of perforation, patients with stents should not receive ramucirumab [level III].
- Other active second-line agents include taxanes and irinotecan (if not used in the first line) and single-agent ramucirumab [level I].
- When applicable, clinical trials should be considered at all stages of care [level III].
- If performance status permits, elderly patients with gastric cancer should be considered for systemic chemotherapy [level III].
- The role of immunotherapy with PD-1–targeted agents in advanced gastric cancer is evolving [level I].

Evidence Summary

The management of metastatic gastric cancer is an increasingly common requirement, because many patients are diagnosed with, or ultimately relapse into, advanced disease. The primary focus of care should be symptom relief, with the involvement of a multidisciplinary team, including palliative care. Clinical trials are now ongoing [EPIC-1511 (see NCT02853474 at http://ClinicalTrials.gov)] to determine whether early palliative care will improve quality of life and survival, as in metastatic lung cancer[5].

A systematic review and meta-analysis has demonstrated a significant OS benefit for systemic chemotherapy compared with BSC in advanced gastric cancer [hazard ratio (HR): 0.39; 95% confidence interval (CI): 0.28 to 0.52], with the survival benefit being greater for combination regimens than for single-agent chemotherapy (HR: 0.83; 95% CI: 0.74 to 0.93)[6,7]. Combination chemotherapy should therefore be considered for all patients with metastatic gastric cancer and adequate performance status (Eastern Cooperative Oncology Group ≤ 2), with equal consideration for systemic treatment given to fit elderly patients[8]. Outside of clinical trials, which should be considered for all patients when appropriate, many chemotherapy regimens are acceptable, with upfront HER2 testing required to guide the selection of first-line regimens in particular.

Webb *et al.*[9] established epirubicin–cisplatin–fluorouracil (ECF) as a standard of care for the first-line treatment of metastatic gastric cancer (median survival: 8.9 months). The REAL-2 noninferiority trial subsequently randomized previously untreated patients to 4 different epirubicin-based regimens—ECF, EOF (epirubicin–oxaliplatin–fluorouracil), ECX (epirubicin–cisplatin–capecitabine), EOX (epirubicin–oxaliplatin–capecitabine)—to compare capecitabine with fluorouracil and oxaliplatin with cisplatin. Median OS for the regimens ranged from 9.3 months to 11.2 months, with the capecitabine and oxaliplatin regimens found to be as effective as the standard fluorouracil and cisplatin regimens[10]. The ML 17032 noninferiority trial showed that cisplatin–capecitabine (CX) was as effective as standard cisplatin–fluorouracil (CF) in terms of progression-free survival [PFS (5.6 months vs. 5.0 months; HR: 0.81; 95% CI: 0.63 to 1.04; $p < 0.001$, with a noninferiority margin of 1.25)] and OS (10.5 months vs. 9.3 months; HR: 0.85; 95% CI: 0.64 to 1.13; $p = 0.008$, with a noninferiority margin of 1.25)[11]. A meta-analysis of the REAL-2 and ML 17032 trials does, however, suggest that OS is superior for capecitabine-based regimens compared with fluorouracil-based regimens[12].

Although fluoropyrimidine and platinum–based regimens are most commonly used, a reasonable option for patients who are unable to tolerate platinum-based chemotherapy is leucovorin–fluorouracil–irinotecan (FOLFIRI), which, in a recent phase III study, resulted in response rates, PFS, and OS equivalent to those with ECF[13]. The combination of docetaxel–cisplatin–fluorouracil (DCF) has also been shown to be an effective regimen, resulting in improved response rates, time to progression, and OS compared with those achieved with CF[14]. However, toxicity is significantly greater with DCF, and so dose-modified DCF or other DCF modifications are preferred[15]. Other reasonable first-line chemotherapy options for metastatic gastric cancer include leucovorin–fluorouracil–oxaliplatin (FOLFOX)[16] and capecitabine–oxaliplatin (XELOX)[17,18]. Overall, however, strong consideration should be given to treatment toxicity and to patient preference and convenience when selecting a suitable therapy.

The TOGA trial established trastuzumab in combination with fluoropyrimidine–cisplatin chemotherapy as the standard first-line therapy for the 10%–20% of advanced gastric adenocarcinomas that are HER2-positive[19]. In addition to improved response rates and PFS, median OS was significantly prolonged in patients treated with trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) compared with chemotherapy alone (13.8 months vs. 11 months, $p = 0.046$). However, benefits were greatest in patients with HER2 IHC scores of 3+ or 2+ with evidence of *HER2* gene amplification on fluorescence *in situ*

hybridization analysis (median OS: 16 months)[19]. Currently, dual HER2 blockade has no role in HER2-positive metastatic gastric cancer, given that the results of the phase III JACOB study failed to show a statistically significant survival advantage with the addition of pertuzumab to trastuzumab and chemotherapy[20].

The benefit of second-line chemotherapy for suitable, fit patients has been demonstrated in numerous clinical trials[7]. Among the active agents in this setting is ramucirumab, the vascular endothelial growth factor receptor antibody. In the REGARD trial, OS was significantly improved when patients who had progressed on previous first-line therapy received single-agent ramucirumab than when they received placebo (5.2 months vs. 3.8 months, $p = 0.047$)[21]. Another study looked at the combination of ramucirumab and paclitaxel compared with paclitaxel alone and found, for the combination, a significant improvement in the response rate (28% vs. 16%, $p = 0.0001$), PFS (4.4 months vs. 2.9 months; HR: 0.64; $p < 0.0001$), and OS (9.6 months vs. 7.4 months; HR: 0.81; $p = 0.017$)[22].

Irinotecan has also shown activity in the second-line setting as a single agent and in combination with leucovorin and fluorouracil (FOLFIRI) for patients who have not received a fluoropyrimidine in the first line[23,24]. In a study comparing single-agent irinotecan with single-agent paclitaxel, no difference was found between the treatments for PFS (2.3 months vs. 3.6 months, $p = 0.33$) or OS (8.4 months vs. 9.5 months, $p = 0.38$)[25]. Compared with BSC, single-agent irinotecan was associated with a significantly reduced risk of death (HR: 0.48; 95% CI: 0.25 to 0.92; $p = 0.012$) and improved tumour-related symptoms[26]. Finally, as with single-agent paclitaxel, data also support the use of single-agent docetaxel: a randomized trial comparing docetaxel with BSC showed improvements in OS and tumour-related symptoms[27].

The role of immunotherapy in gastric cancer is also rapidly evolving. The PD-1–targeted agents such as nivolumab and pembrolizumab are set to become additional treatment options for previously treated—and possibly newly diagnosed—advanced metastatic gastric cancer. Their use follows from recent phase III data in a study that compared nivolumab with placebo in previously treated metastatic gastric cancer, showing a significant improvement in OS with nivolumab (5.3 months vs. 4.1 months; HR: 0.62; 95% CI: 0.50 to 0.76; $p < 0.0001$)[28]. Preliminary data from a phase II study of pembrolizumab in newly diagnosed and previously treated metastatic gastric cancer has shown promising activity, with salvage treatment in particular demonstrating a response rate of 16% in tumours expressing PD-1 ligand[29].

RECTAL CANCER

Question 1

What are the recommendations for the use of short-course compared with long-course preoperative radiation for rectal cancer?

- With studies showing similar local control and OS, short-course preoperative radiotherapy can be considered over long-course preoperative radiotherapy with concurrent chemotherapy for disease in which the resection margin is predicted to be clear [level I].
- For patients who require downstaging, but who are not fit for chemotherapy, short-course radiation followed by delayed surgery is an option [level III].
- All patients should, however, be discussed in a multidisciplinary setting that includes surgical, medical, and radiation oncologists and radiologists, with consideration given to the need for tumour downsizing, potential treatment toxicity, and patient preference and convenience [level III].
- Participation in clinical trials is encouraged [level III].

Evidence Summary

Rectal cancers carry an increased risk of local recurrence, which is associated with considerable morbidity and mortality. Significant emphasis is therefore given to treatment modalities that reduce the risk. Those modalities include total mesorectal excision for all stages other than very early T1 cancers, in addition to neoadjuvant or adjuvant radiation or chemotherapy (or both). Indeed, those techniques have helped to reduce the risk of local recurrence by more than 50%.

With respect to radiation, the standard approach in North America has been long-course preoperative radiation to a total dose of 50.4 Gy (1.8 Gy in 28 fractions) delivered over 5–6 weeks, typically with concurrent radiosensitizing chemotherapy, followed by curative surgery 4–8 weeks later. To date, numerous trials and meta-analyses have compared that strategy with postoperative chemoradiation, showing better tolerability and compliance, as well as improved local control and surgical outcomes, with preoperative chemoradiation. However, no improvement in OS has been demonstrated with preoperative chemoradiation[30–32].

An alternative approach favoured in Europe involves short-course high-dose preoperative radiation: 25 Gy given in 5 fractions delivered over 5 days, without concurrent chemotherapy, followed by immediate curative surgery. Several studies have compared preoperative short-course radiotherapy and immediate surgery with surgery alone, showing consistent improvements in local control[33–35]. Only one trial, the Swedish Rectal Cancer Trial, demonstrated a survival benefit[33]. In that study, after a median follow-up of 13 years (range: 3–15 years), the OS rates, at 38% and 30%, and the cancer-specific survival rates, at 72% and 62%, favoured radiotherapy. Two key randomized trials by groups in Poland and Australia–New Zealand compared preoperative short-course radiotherapy followed by immediate surgery with preoperative long-course chemoradiotherapy and found no difference in local recurrence or OS[36,37]. Furthermore, a recent meta-analysis of studies comparing preoperative short- compared with long-course radiation in rectal cancer, which included the foregoing trials, confirmed the equivalence of the two techniques by showing no difference in sphincter preservation, complete resection (R0) rate, local recurrence, or OS. Long-course radiation was, however, associated with greater tumour downstaging and an improved rate of pathologic complete response, but also with greater acute toxicity[38].

Another variation of the preoperative short-course radiation strategy involves delayed rather than immediate surgery, which has been found in retrospective studies to be well tolerated, with greater tumour regression rates[39–41].

A recent randomized prospective study confirmed those findings by demonstrating that preoperative long-course radiotherapy alone, coupled with delayed conventional surgery, and preoperative short-course radiotherapy, coupled with immediate (within 1 week) or delayed (within 4–8 weeks) surgery, are noninferior in terms of local and distant recurrence, OS, and postoperative complications[42]. Furthermore, patients treated with short-course radiation and delayed surgery experienced a significantly higher rate of pathologic complete response[43].

A concern with preoperative short-course radiation and delayed surgery is that chemotherapy will also be delayed, which might, compared with conventional preoperative long-course chemoradiation, compromise systemic control. Studies are now looking at combining short-course radiation and delayed surgery with full-dose chemotherapy during the waiting period before surgery. In one such study, 515 patients with fixed T3–4 tumours were randomized to preoperative long-course chemoradiation or to short-course radiation followed by consolidative chemotherapy before surgery. The groups showed no differences in the rate of complete resection (R0), pathologic complete response, postoperative complications, local failure, or distant metastasis. However, in the short-course group, the acute toxicity rate was significantly lower, and OS was improved[44]. Results from the ongoing RAPIDO trial are awaited to provide additional information about this new approach[45].

Overall, preoperative radiation remains a cornerstone in the management of resectable rectal cancer, with a critical role in reducing local recurrence rates. However, the format in which it is delivered is evolving, with an increasingly selective role for conventional preoperative long-course radiation with concurrent chemotherapy, given its significant demand on time and resources, and its increased toxicity. Preoperative short-course radiation followed by immediate surgery is appropriate for patients with rectal cancer when magnetic resonance imaging predicts a clear circumferential resection margin and no pelvic disease beyond the mesorectum. However, conventional long-course chemoradiation remains the standard of care when tumour downstaging might be required to improve surgical outcomes. Short-course radiation and delayed curative surgery provides an option for larger tumours in which downstaging is required when patients are unfit for chemotherapy. Emerging evidence suggests that short-course radiation followed by consolidative chemotherapy before definitive surgical management might replace long-course chemoradiotherapy as the new standard of care for patients with locally advanced disease. All treatment decisions should, however, involve a multidisciplinary team discussion to determine the optimal management strategy.

COLORECTAL CANCER

Question 1

What are the currently available options for the management of colorectal peritoneal carcinomatosis?

- Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) should be considered in selected patients with colorectal peritoneal carcinomatosis [level I].
- The best results are seen in patients with limited peritoneal disease (for example, peritoneal cancer index < 20) when complete cytoreduction can be achieved [level II].
- Patients should be reviewed by a multidisciplinary team including surgeons, medical oncologists, and pathologists with experience in treating patients with peritoneal carcinomatosis [level III].
- However, further clinical trial data are needed—specifically, data relating to the need for, and the technical details of CRS and HIPEC, appropriate patient selection, and the need for neoadjuvant and adjuvant chemotherapy in conjunction with CRS and HIPEC [level III].

Evidence Summary

Peritoneal carcinomatosis occurs in approximately 20% of patients with metastatic CRC, and it is a poor prognostic factor associated with a significantly reduced median survival (<6 months without treatment)[46–48]. Options for management include BSC or palliative systemic chemotherapy, with the median survival being in the 12- to 24-month range regardless of the specific CRC regimen used[49]. However, as a result of the work of Dr. Paul Sugarbaker and others, there is now an expanding role for more aggressive management, in select patients, involving peritoneal CRS and HIPEC[50].

The goal of CRS is to resect all visible macroscopic peritoneal disease. The exact surgical procedure performed is guided by the extent of peritoneal disease as defined by the peritoneal cancer index[51]; however, a typical CRS will involve peritoneal stripping and omentectomy, with additional procedures including one or more of cholecystectomy, colectomy, hysterectomy, oophorectomy, gastrectomy, and splenectomy as required. A score is then given to define the success of the resection (for example, completeness of cytoreduction score), the goal being maximal cytoreduction with no residual disease (score of 0)[51]. After complete or near-complete CRS, HIPEC is delivered intraoperatively, together with a heating perfusion system. The role of hyperthermia is to increase the cytotoxicity of the chemotherapy, which is typically single-agent mitomycin C or oxaliplatin[52].

The initial retrospective studies of CRS and HIPEC in the management of peritoneal carcinomatosis from metastatic CRC resulted in an impressive median OS of 15–36 months, with 5-year survival rates in the 23%–47% range[53–56]. Those results led to a prospective study in which 105 patients with CRC carcinomatosis, but without distant metastatic disease, were randomized to receive palliative chemotherapy ($n = 51$) or CRS and HIPEC with mitomycin C ($n = 54$). The OS at the 8-year final follow-up favoured CRS and HIPEC (12.6 months vs. 22.2 months, $p = 0.028$), with the greatest benefit obtained in patients with a lower burden of disease and in those experiencing a complete resection with no residual disease (5-year survival: 45%)[57,58]. Real-world multicentre retrospective data have demonstrated similar results for CRS and intraperitoneal chemotherapy in CRC carcinomatosis, with a median OS between 19 months and 30 months, and a 5-year survival rate between 19% and 27%—the best results being observed in patients with limited peritoneal

disease who experienced a complete resection[59,60]. Indeed, if treatment is limited to those with a low burden of disease to facilitate a higher rate of complete resection, a median os of 41 months with a 5-year survival exceeding 40% can be achieved[61].

Based on those data, some authors have written that systemic therapy alone is no longer appropriate for patients with limited peritoneal carcinomatosis from crc[62]. However, the technique remains controversial, and only a limited (but expanding) number of centres in Canada offer it. That slow adoption contrasts with the technique of hepatic metastasectomy, which has become a more accepted standard of care for select patients with metastatic crc involving the liver. Studies comparing crs and hipec with hepatic metastasectomy in advanced crc have shown similar survival, morbidity, and mortality, particularly if patients are stratified by the completeness of the hepatic or peritoneal resection[63]. Notably, mortality with crs and intraperitoneal chemotherapy is typically less than 5% and largely secondary to abdominal sepsis; morbidity is in the 20% range and is related to the formation of fistulae and abscesses and the need for reoperation[64].

Although crs with intraperitoneal chemotherapy is currently not a standard of care for all patients with crc carcinomatosis, it should be considered in select patients, with multidisciplinary review to determine its ultimate suitability based on multiple factors including peritoneal disease burden (peritoneal cancer index > 20 is considered extensive disease), likelihood of achieving complete resection, and performance status (Eastern Cooperative Oncology Group ≤ 2). However, future studies and clinical trials are required to better define patient selection criteria to ensure that those who undergo the procedure are likely to benefit. Furthermore, many technical questions remain, including the actual need for hipec after crs, and if hipec is performed, the optimal chemotherapy agent or agents to use. Finally, ongoing studies are looking at the role of crs and intraperitoneal chemotherapy in the adjuvant setting as preventive therapy in patients at high risk of developing carcinomatosis[65].

Question 2

How can patients and families who should be referred for genetic assessment for hereditary crc be identified, and how should such patients be managed?

- Recognition of hereditary crc is important so that patients and families at risk of hereditary crc receive genetic screening and appropriate clinical screening, early diagnosis, and treatment [level iii].
- However, a multidisciplinary team including a genetic counsellor and a dedicated genetics program must be in place [level iii].
- Genetic screening can be performed in a number of ways depending on the clinical situation; the method should be selected in conjunction with a cancer genetics expert [level iii].

Evidence Summary

Approximately 3%–5% of crcs are associated with germline mutations that confer a predisposition to hereditary crc. Prompt identification of individuals at risk for hereditary crc is important for both the individual and the family because it facilitates earlier screening, diagnosis, and treatment, and consequently, improved outcomes. Hereditary crc is broadly divided into non-polyposis and polyposis syndromes. Key non-polyposis syndromes include Lynch syndrome and familial crc type X; the common polyposis syndromes include fap and *MUTYH*-associated polyposis. Although an in-depth discussion of hereditary crc syndromes is beyond the scope of this guideline, the brief description of the key syndromes that follows is meant to aid in the identification of high-risk patients.

Lynch syndrome (hereditary non-polyposis colon cancer) is an autosomal-dominant disorder caused by germline mutations in one of the mismatch repair (mmr) genes (*MLH1, MSH2, MSH6, PMS2,* or *EPCAM)* that predispose to tumours with dna microsatellite instability (msi) that can demonstrate loss of expression of the corresponding mmr protein by ihc[66]. The lifetime risk for crc in Lynch syndrome is 30%–70%, and women also have a 30%–60% lifetime risk of endometrial cancer[67]. Other less-common cancers associated with the syndrome include those of the ovary, urinary tract, small intestine, stomach, and pancreas[67]. At-risk patients requiring genetic testing can be identified using the Amsterdam ii criteria[68] or the revised Bethesda guidelines[69]. Patients meeting Amsterdam ii criteria, but without evidence of mmr mutations, are classified as familial crc type X and are at risk for crc but not for the other extracolonic Lynch-associated cancers[70].

The most common hereditary polyposis syndrome is fap, which is associated with germline mutations in the *APC* tumour suppressor gene, resulting in the presence of thousands of adenomas in the colon and rectum, carrying a lifetime risk of crc in excess of 90%[66]. Extracolonic features include gastric and duodenal polyps, thyroid and brain tumours, and supernumerary teeth, among others[71]. Notably, attenuated fap is a variant of fap that is usually associated with fewer colorectal polyps (≥20, ≤100), which typically develop later in life and which are associated with a variable, but lower, risk of crc[72]. However, some families with attenuated fap have polyp numbers varying from fewer to 10 into the thousands, and possible early age at onset[73]. *MUTYH*-associated polyposis is also characterized by multiple colorectal polyps (<100), but with an autosomal-recessive pattern of inheritance and an age of onset in the mid-50s[74].

Patients at risk of hereditary crc can be identified by recognition of features in their medical history or presentations that are associated with specific hereditary cancer syndromes as outlined, or in the case of suspected Lynch syndrome, fulfilment of the Amsterdam ii criteria[68]. Other features that could be suggestive of a hereditary crc syndrome include earlier age at onset, multiple primaries, multifocal (bilateral) disease (synchronous or metachronous), or family history of the same or an unrelated tumour.

All patients at high risk for a hereditary crc should be referred for further confirmatory testing. That referral might include testing for specific founder gene mutations in those with a known family history of hereditary crc. Alternatively, testing might be directed by the suspected crc syndrome—for example, testing for mmr deficiency in suspected Lynch syndrome, or *APC* gene mutations

in suspected FAP. Alternatively, local or commercial gene mutation panels could be used. In the case of Lynch syndrome, recent data have shown increased diagnostic sensitivity with universal testing of all CRCs for MMR deficiency, diagnosed by IHC-confirmed loss of MMR protein expression, with subsequent sequencing of the affected or lost MMR gene to confirm the presence of the mutation. Recommendations for universal testing vary by province, because emphasis is placed on ensuring that, at the least, all individuals suspected of having Lynch syndrome because of positive Amsterdam II criteria or revised Bethesda guidelines, or those with evidence of MSI via IHC, are referred for further testing.

The screening protocol required is also dictated by the specific hereditary CRC syndrome, which highlights the importance of early confirmatory testing and diagnosis, with involvement of expert groups to guide optimal screening practices related not only to CRC but also to the other potentially associated cancers. Overall, however, it is of utmost importance that comprehensive care for suspected and confirmed hereditary CRC be provided by a multidisciplinary team including a genetic counsellor to support patients and to guide testing, screening, and follow-up.

Question 3

Should primary tumour location (PTL) affect the treatment of metastatic CRC?

- Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of a biologic for first-line treatment decisions [level III].
- In patients with *RAS* wild-type (WT) left-sided CRC, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an epidermal growth factor receptor (EGFR) monoclonal antibody [mAb (cetuximab or panitumumab)] is recommended in the first-line setting [level I, based on retrospective subset analyses of prospective randomized trials with subsequent meta-analyses of those retrospective analyses for first-line recommendations].
- In patients with *RAS* WT right-sided colorectal cancer, first-line EGFR mAbs are not recommended. The combination of bevacizumab with standard chemotherapy remains the standard of care for those patients [level III].
- At this time, there is no evidence to recommend the selective use of EGFR mAbs in the second-line setting based on PTL [level III].
- In the second-line setting, patients who have not been treated with bevacizumab in the first-line should be offered bevacizumab in combination with standard chemotherapy [level I].
- In the third-line setting, all *RAS* WT patients who have not previously been treated with an EGFR mAb should be offered one [level I].
- At this time, evidence for the selective use of EGFR mAbs based on PTL, where tumour response is the primary goal of therapy, is insufficient [level I].

Evidence Summary

In Canada, CRC is the 2nd most common cancer, accounting for 13% of all cancers[75]. Despite recent advances in the management of CRC, it still represents the 2nd most common cause of cancer death for men and the 3rd most common cause of cancer death for women[75]. Initial management of unresectable metastatic CRC involves a combination of systemic chemotherapy (fluorouracil–leucovorin with either irinotecan or oxaliplatin) and mAb therapies targeting either vascular endothelial growth factor receptor or EGFR. The reported OS for advanced CRC with those treatments ranges from 24 months to 32 months[75,76].

Because of the heterogeneity of the disease in terms of prognosis and response to treatment, PTL has been thought to play a major role as a prognostic and predictive marker. That role might be attributable to multiple factors, including clinical, molecular, and microbiome differences related to the side of the colon[77–81]. A recent systematic review and meta-analysis showed that PTL has prognostic value and that the risk of death is significantly lower in left-colon cancer [LCC (HR: 0.82; 95% CI: 0.79 to 0.84; $p < 0.001$)][82]. The analysis included sixty-six trials and 1.4 million patients, and its results were independent of ethnicity, disease stage, and type of study. The meta-analysis concluded that PTL should be established as a key criterion for confirming OS outcomes in all stages of CRC.

Another meta-analysis has considered patients with unresectable *RAS* WT metastatic CRC[83]. It included six randomized trials (CRYSTAL, FIRE-3, Cancer and Leukemia Group B 80405, PRIME, PEAK, and 20050181) that compared chemotherapy plus EGFR mAb therapy (experimental arm) with chemotherapy alone or chemotherapy–bevacizumab (control arms). Primary tumour location and *RAS* mutation status were available for 2159 of the 5760 patients. A significantly worse prognosis was observed for patients with right-colon cancer (RCC) than for those with LCC in both the pooled control and experimental arms [OS HR: 2.03 (95% CI: 1.69 to 2.42) and 1.38 (95% CI: 1.17 to 1.63) respectively; PFS HR: 1.59 (95% CI: 1.34 to 1.88) and 1.25 (95% CI: 1.06 to 1.47) respectively; and overall response rate (ORR) HR: 0.38 (95% CI: 0.28 to 0.50) and 0.56 (95% CI: 0.43 to 0.73) respectively]. In addition to the differences in prognosis based on PTL, the Arnold meta-analysis[83] also revealed that PTL has predictive value, with a significant benefit for chemotherapy plus EGFR mAb therapy observed in patients with LCC (OS HR: 0.75; 95% CI: 0.67 to 0.84; PFS HR: 0.78; 95% CI: 0.70 to 0.87), but not for those with RCC (OS HR: 1.12; 95% CI: 0.87 to 1.45; PFS HR: 1.12; 95% CI: 0.87 to 1.44; p for interaction: <0.001 and 0.002 respectively). For ORR, a trend (p for interaction: 0.07) toward a greater benefit from chemotherapy plus EGFR mAb therapy was observed in patients having LCC (odds ratio: 2.12; 95% CI: 1.77 to 2.55) than in those having RCC (odds ratio: 1.47; 95% CI: 0.94 to 2.29)[83].

Holch *et al.*[78] conducted a meta-analysis of first-line clinical trials (thirteen randomized controlled trials and one prospective pharmacogenetics study) in patients with metastatic CRC to assess the relevance of PTL in terms of prognostic and predictive value. The data clearly indicate that, compared with LCC, RCC is associated with an inferior prognosis. In the random-effects model for OS, that difference was reflected in a clinically relevant HR of 1.56 (95% CI: 1.43 to 1.70; $p < 0.0001$)[78]. The meta-analysis of the PRIME and CRYSTAL studies suggests that PTL is predictive of survival benefit with the addition of an anti-EGFR mAb to

standard chemotherapy in patients with *RAS* WT tumours (OS HR for LCC: 0.69; 95% CI: 0.58 to 0.83; $p < 0.0001$; OS HR for RCC: 0.96; 95% CI: 0.68 to 1.35; $p = 0.802$). The meta-analysis of FIRE-3/Arbeitsgemeinschaft Internistische Onkologie KRK0306, Cancer and Leukemia Group B/SWOG 80405, and PEAK studies indicated that patients with *RAS* WT LCC obtained a significantly greater survival benefit from anti-EGFR treatment than from anti–vascular endothelial growth factor treatment added to standard chemotherapy (HR: 0.71; 95% CI: 0.58 to 0.85; $p = 0.0003$). By contrast, in patients with RCC, benefit from standard therapy was poor, and bevacizumab-based treatment was associated with numerically longer survival (HR: 1.3; 95% CI: 0.97 to 1.74; $p = 0.081$).

A recent retrospective cohort study (based on the Ontario Cancer Registry) compared monotherapy (panitumumab) with combination therapy (cetuximab–chemotherapy) using a primary outcome of OS by PTL in refractory metastatic CRC[84]. For RCC, the median OS was 29.5 months with panitumumab (95% CI: 26.9 months to 32.0 months) and 34.7 months with combination therapy (95% CI: 28.2 months to 40.6 months). For LCC, the median OS was 38.2 months with panitumumab (95% CI: 36.1 months to 41.3 months) and 40.2 months with combination therapy (95% CI: 37.8 months to 43.7 months). Although the study confirmed the prognostic value of PTL, it remains premature to make decisions about single-agent or combination therapy based on those data.

Question 4

What molecular markers are currently available to assist in the management and treatment of patients with CRC?

- In patients considered appropriate for treatment
  - with advanced CRC:
    - Extended *RAS* and *BRAF* V600E testing should be performed in a timely manner for patients with metastatic CRC, preferably based on the metastatic lesion or the most recent formalin-fixed tissue available. A surgical sample or core biopsy is preferred to a cytology sample obtained by fine-needle aspiration [level III].
  - regardless of stage or age:
    - All patients with CRC should undergo MMR testing by IHC.
    - Patients who are MMR-deficient (MSH2- or MSH6-deficient, or MLH1-deficient and BRAF WT) should receive follow-up with genetics to rule out Lynch syndrome [level III].

Evidence Summary

The pathogenesis of CRC involves the accumulation of genetic and epigenetic modifications that regulate proliferation, apoptosis, and angiogenesis[85,86]. Advances in molecular biology since the late 1990s have helped to identify and understand the mechanism of colorectal carcinogenesis. In metastatic CRC, EGFR and the downstream MAPK pathways play a major role in disease progression and have led to the development of multiple targeted therapies[87]. Colorectal cancer can be classified according to molecular markers. The current conventional molecular tests used when evaluating CRC patients include MSI analysis and *BRAF* and *KRAS* mutation analysis[88]. Those markers can have predictive or prognostic value (or both).

One of three members of the RAF (rapidly accelerated fibrosarcoma) serine/threonine protein kinase family, BRAF is a downstream target of KRAS[88]. *BRAF* activating mutations occur in fewer than 10% of patients with sporadic colon cancer[85,89]. *BRAF* mutations in the 600th codon (V600E) represent 80% of *BRAF* mutations and lead to constitutive activation of the BRAF protein and downstream elements of the MAPK cascade[90].

BRAF mutations are found in various types of cancer[91]. As shown in a meta-analysis by Yuan *et al.*[92], it is associated with poor prognosis in metastatic CRC. Twenty-one trials including 5229 patients were identified for the meta-analysis. Of 4616 patients with known *BRAF* status, 343 (7.4%) had *BRAF* mutations. Compared with their counterparts having mutant *BRAF,* patients with *BRAF* WT had a decreased risk of progression and death and better PFS (HR: 0.38; 95% CI: 0.29 to 0.51) and OS (HR: 0.35; 95% CI: 0.29 to 0.42)[92]. As shown in a retrospective cohort study by Jones *et al.*[93], prognosis tends to be better in patients with non-V600E *BRAF* mutation than in those with V600E.

BRAF mutation has not been shown to have predictive value in terms of response to the addition of mAbs to chemotherapy. A meta-analysis by Pietrantonio *et al.*[94] [nine phase III trials and one phase II trial (six first-line and two second-line trials, plus two trials involving chemotherapy-refractory patients)] included 463 patients with *RAS* WT, *BRAF*-mutant CRC. Overall, compared with control regimens, the addition of cetuximab or panitumumab treatment in the *BRAF*-mutant subgroup did not significantly improve PFS (HR: 0.88; 95% CI: 0.67 to 1.14; $p = 0.33$), OS (HR: 0.91; 95% CI: 0.62 to 1.34; $p = 0.63$), or ORR (relative risk: 1.31; 95% CI: 0.83 to 2.08; $p = 0.25$)[94]. Another meta-analysis by Rowland *et al.*[87] included seven randomized controlled trials that met the inclusion criteria for assessment of OS and eight trials that met the inclusion criteria for assessment of PFS. For *RAS* WT, *BRAF*-mutant tumours, the HR for OS benefit with anti-EGFR mAbs was 0.97 (95% CI: 0.67 to 1.41); the HR for *RAS* WT, *BRAF* WT tumours was 0.81 (95% CI: 0.70 to 0.95). However, the test of interaction ($p = 0.43$) was not statistically significant, highlighting the possibility that the observed differences in the effect of anti-EGFR mAbs on OS according to the *BRAF* mutation status might be attributable to chance alone. With respect to the PFS benefit with anti-EGFR mAbs, the HR was 0.86 (95% CI: 0.61 to 1.21) for *RAS* WT, *BRAF*-mutant tumours and 0.62 (95% CI: 0.50 to 0.77) for *RAS* WT, *BRAF* WT tumours (test of interaction, $p = 0.07$)[87].

Vemurafenib is BRAF kinase inhibitor that had been approved for metastatic melanoma with the *BRAF* V600E mutation. A randomized phase II trial by Kopetz *et al.*[95] compared the combination of irinotecan–cetuximab with or without vemurafenib in patients with *BRAF* V600E mutations and extended *RAS* WT metastatic CRC. Patients had received 1 or 2 prior regimens, with no prior anti-EGFR agents. The study enrolled 106 patients (54 in the experimental arm). The addition of vemurafenib was associated with improved PFS (HR: 0.42; 95% CI: 0.26 to 0.66; $p < 0.001$), with the median PFS duration being 4.4 months (95% CI: 3.6 months to 5.7 months) compared with 2.0 months (95% CI:

1.8 months to 2.1 months). The response rate was 16% compared with 4% ($p = 0.09$), and the disease control rate was 67% compared with 22% ($p < 0.001$)[95]. Another phase II trial evaluated the activity and safety of FOLFOXIRI (leucovorin–fluorouracil–oxaliplatin–irinotecan) with or without panitumumab in patients primarily with nonresectable metastatic *RAS* WT CRC. The primary endpoint was ORR. Of 96 patients, 16 had a *BRAF* mutation. The addition of panitumumab to FOLFOXIRI was associated with an increased ORR, and in patients with *BRAF* V600E mutations, the ORRs were 71.4% for FOLFOXIRI plus panitumumab and 22% for chemotherapy alone[96]. No consensus statement could be made based on that limited evidence.

Mutations in genes involved in the DNA mismatch repair (MMR) system *(MLH1, MSH2, MSH6,* and *PMS2)* result in alterations in highly repeated DNA sequences (microsatellites)[88]. This MSI can be found in about 15% of patients with CRC, with 3% being associated with Lynch syndrome, and the other 12% being caused by sporadic acquired hypermethylation of the promoter of the *MLH1* gene[97]. The distinctive features of CRCs with MSI-high status include a tendency to arise in the proximal colon and a poorly differentiated, mucinous, or signet-ring appearance, with a higher mutational burden and tumour neoantigen load and, consequently, dense immune cell infiltration. Overall, these tumours have a slightly better prognosis[97], and MSI-high status is therefore considered a possible marker for OS and disease-free survival, and for lack of benefit with single-agent fluorouracil in the adjuvant setting of stage II colon cancer[91].

A phase II trial evaluated the clinical activity of pembrolizumab, an anti–PD-1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinoma (of various origins) with or without MMR deficiency. The immune-related ORR and immune-related PFS rates were, respectively, 40% (4 of 10 patients) and 78% (7 of 9 patients) for MMR-deficient CRCs and 0% (0 of 18 patients) and 11% (2 of 18 patients) for MMR-proficient CRCs. The response in patients with MMR-deficient non-CRC was similar to that in patients with MMR–deficient CRC [immune-related ORR: 71% (5 of 7 patients); immune-related PFS: 67% (4 of 6 patients)][98]. Another phase II trial evaluated the role of the PD-1 inhibitor nivolumab in patients with MMR-deficient, MSI-high metastatic CRC. The primary endpoint was investigator-assessed ORR. The trial included 74 patients, and at a median follow-up of 12 months, 23 of 74 patients (31.1%; 95% CI: 20.8% to 42.9%) achieved an investigator-assessed objective response, and 51 patients (69%; 95% CI: 57% to 79%) experienced disease control for 12 weeks or longer[99].

The HER2 transmembrane receptor tyrosine kinase is a member of the EGFR family. Activation of HER2 plays a key role in cell proliferation, cell differentiation, inhibition of apoptosis, and tumour progression[100]. Several trials tried to assess the overexpression of HER2 in the gastrointestinal tract, with results ranging from 0%–83%, the wide range being thought to be a result of differences in methods and reagents used for the tests[101]. A recent review of 8874 patients with metastatic CRC assessed the presence of HER2 using hybrid-capture-based comprehensive genomic profiling, finding HER2 amplifications and short-variant alterations, or both, in 433 members (4.9%) of the cohort[102].

A phase II clinical trial assessed the role of dual anti-HER2 targeted therapy with trastuzumab and lapatinib in the management of refractory metastatic CRC. The trial enrolled patients with *KRAS* exon 2 (codons 12 and 13) WT and HER2-positive metastatic CRC refractory to the standard of care. Only 27 patients were eligible for the dual treatment. Of those patients, 8 achieved an objective response (30%; 95% CI: 14% to 50%), with 1 patient achieving a complete response (4%; 95% CI: –3% to 11%). The remaining 7 patients achieved a partial response (26%; 95% CI: 9% to 43%). Stable disease was maintained in 12 patients (44%; 95% CI: 25% to 63%)[103].

ACKNOWLEDGMENTS

The Planning Committee for the 2017 annual Eastern Canadian Gastrointestinal Cancer Consensus Conference thank the following organizations for their unrestricted educational support: Amgen, Celgene Canada, Ipsen, Pfizer, Roche, Shire, Eli Lilly, Taiho, and Novartis.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: DA is a member of advisory boards for Celgene and Shire, and has received grants or honoraria from Celgene and Amgen. TA is a member of advisory boards for Amgen, Novartis, Ipsen, Celgene, and Shire, and has received grants or honoraria from Novartis, Roche, and Boehringer Ingelheim. SB is a member of advisory boards for Eli Lilly and Amgen. PC was a one-time advisory board member for AstraZeneca and Merck in 2017, Pfizer and Eli Lilly in 2016, and Celgene, Sanofi, and Boehringer Ingelheim in 2015. BC is a member of advisory boards for Celgene and Novartis, and a member of a speakers bureau for Novartis. SG is a member of advisory boards for Bayer, Roche, Pfizer, Astellas, and Novartis, and her institution has received funding from Bristol–Myers Squibb and Amgen for a clinical trial in which she is listed as an investigator. JG has received grants and honoraria from Novartis. MH is a member of advisory boards for Amgen, Roche, Novartis, Celgene, and Pfizer, and has received grants or honoraria from Novartis and Astellas. DJ's institution has received funding from AstraZeneca, Bristol–Myers Squibb, Roche, Esperas, Pfizer, Corvus, Turnstone Biologics, Merck, Boston Biomedical, and Array, for clinical trials in which he is listed as an investigator. PK has received grants or honoraria from Pfizer, Celgene, and Shire. EP is a member of advisory boards for Amgen, Novartis, and Genomic Health, and has received grants and honoraria from Roche. RR is a member of a speakers bureau for Astellas, Merck, Roche, Eli Lilly, AstraZeneca, and Bristol–Myers Squibb, and has received grants or honoraria from Celgene, Amgen, and Novartis. MR is a member of advisory boards for, and has received grants or honoraria from, Jensen and Novartis. MS is a member of advisory boards for Shire and Pfizer, and has received grants and honoraria from Amgen. LS is a member of the American College of Surgeons Rural Surgery Advisory Counsel. ESH is a member of advisory boards for Celgene, Bristol–Myers Squibb, Novartis, and Merck.

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Canada, North York (Servidio-Italiano); Grand River Regional Cancer Centre, Kitchener (Tsvetkova, Valdes); London Health Sciences Centre, London (Welch); †Newfoundland and Labrador—Dr. H. Bliss Murphy Cancer Centre, St. John's (Ahmad, Armstrong, Powell, Rorke, Seal, Siddiqui, Stuckless); Faculty of Medicine, Memorial University of Newfoundland, St. John's (Green, Seal, Siddiqui, Tate); Faculty of Surgery, Memorial University of Newfoundland, St. John's (Kanagaratnam); Eastern Health Authority, St. John's (MacMillan); Labrador–Grenfell Regional Health Authority, Happy Valley–Goose Bay (Simms, Smithson); ‡Dana–Farber Cancer Institute, Boston, MA, U.S.A.; §Prince Edward Island—Prince Edward Island Cancer Treatment Centre, Charlottetown; ‖Nova Scotia—QEII Health Sciences Centre, Dalhousie University, Halifax; #New Brunswick—Saint John Regional Hospital, Saint John (Gray); Centre hospitalier universitaire Dr-Georges-L.-Dumont, Moncton (Finn, St-Hilaire); Dr. Everett Chalmers Hospital, Fredericton (Raza); Moncton City Hospital (Harb); **Quebec—McGill University Health Centre, Montreal (Kavan, Thirlwell); Centre hospitalier de l'Université de Montréal, Montreal (Tehfé).

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