Eastern Canadian Gastrointestinal Cancer Consensus Conference 2014

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ABSTRACT

The annual Eastern Canadian Colorectal Cancer Consensus Conference was held in Montreal, Quebec, 23–25 October 2014. Expert radiation, medical, and surgical oncologists and pathologists involved in the management of patients with gastrointestinal malignancies participated in presentations and discussions resulting in consensus statements on such hot topics as management of neuroendocrine tumours, advanced and metastatic pancreatic cancer, and metastatic colorectal cancer.

Key Words

Neuroendocrine tumours, pancreatic cancer, colorectal cancer, screening, chemotherapy, radiation therapy, RAS testing


INTRODUCTION

Last year’s Eastern Canadian Colorectal Cancer Consensus Conference (EC5) was held in Montreal, Quebec, 23–25 October 2014. This conference report represents the consensus opinion of oncologists and pathologists from across Eastern Canada on the management of patients with selected gastrointestinal (gi) malignancies.

TERMS OF REFERENCE

Participants

Medical, radiation, and surgical oncologists, pathologists, and gastroenterologists from Eastern Canada involved in the care of patients with gi malignancies who attended EC5 participated in discussions and consensus creation (Table I).

Target Audience

The target audience for this EC5 consensus report are health care professionals involved in the care of patients with gi malignancies. The consensus statements are not intended to replace practice guidelines based on systematic reviews of evidence, but rather to report the evidence-based consensus opinion of attendees at EC5 2014. The objective of the report is “best practice” implementation in the management of patients with neuroendocrine tumours (nets) and pancreatic (pcc) and colorectal (crc) cancers. The report can also be a valuable source of information for program funding decisions by administrators.

Basis of Recommendations

The recommendations presented here are based on evidence from the published literature, meeting presentations, and discussion of the best available evidence¹. Where applicable, references are cited.

These levels of evidence were used in making the recommendations:

I: Evidence from randomized controlled trials
II-1: Evidence from controlled trials 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 and without the intervention (dramatic results from uncontrolled experiments could be included here)

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III: Opinion of respected authorities, based on clinical experience; descriptive studies or expert committee reports

The consensus statements are applicable to a broad patient population and therefore might not be applicable to individual patients; individual decisions should be always be made within a doctor–patient relationship.

NEUROENDOCRINE TUMOURS

What Classification System and Diagnostic Tools Should Be Used in Reporting on NETs?

In addition to the 2009 TNM staging system from the Union for International Cancer Control, we recommend also using the 2010 World Health Organization (WHO) classification of NETs to ensure consistency and to facilitate comparisons of research from various centres. Reporting tumour stage and grade is recommended for all NETs. Tumour grade is based on either or both of the number of mitoses per 10 high-power fields (hpf) counted in the most mitotically active areas, or the proliferative activity measured by immunohistochemistry for the Ki-67 (MIB1) antibody counted in “hot spots” (with the most intense staining). Grade 1 NET includes tumours with fewer than 2 mitoses per 10 hpf or a Ki-67 index of 2% or less; grade 2 NET includes tumours with 2–20 mitoses per 10 hpf or a Ki-67 index of 3%–20%; grade 3 NET includes tumours with more than 20 mitoses per 10 hpf or a Ki-67 index of

TABLE I  Meeting participants

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<tr>
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20% or more. Grade 1 and grade 2 tumours are both considered well-differentiated NETs; grade 3 tumours are poorly differentiated, being either small-cell or large-cell neuroendocrine carcinomas.

- Core biopsy of the tumour is recommended if safe and feasible.
- Baseline blood work [chromogranin A, 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA)] and baseline computed tomography and octreotide imaging are recommended.
- In patients with carcinoid-like symptoms, baseline echocardiography should be considered.
- Imaging with metaiodobenzylguanidine can be considered in selected patients.

**Summary of Evidence**

Neuroendocrine tumours are rare tumours arising from neuroendocrine cells widely distributed throughout the epithelia, including enterochromaffin and enterochromaffin-like cells; D cells; G cells in the gi tract; and β-cells, α-cells, D cells, P cells, and vasoactive intestinal peptide cells in pancreas. The most common sites of origin are the gi tract (64%) and bronchopulmonary system (28%). In Canada, NETs represent about 0.25% of all oncology cases, with the incidence showing a rising trend since the mid-1980s. Factors that hypothetically account for the rise include improvements in pathology evaluation (including the use of immunostaining for molecular markers such as chromogranin A (cga) and synaptophysin), the common use of proton pump inhibitors, an increased rate of endoscopies, and increased clinical awareness.

The classifications of NET have been changing over time. Initially, these tumours were classified based on the site of embryologic origin; the classifications therefore reflected bihistochemical differences. In 1980, WHO adopted classifications that subdivided tumours based on granulostaining technique (for example, gastrin-cell carcinoid, enterochromaffin-cell carcinoid, and so on). The 2010 WHO classification developed a more prognosis-oriented approach, defining NETs as well-differentiated (low grade, G1; and intermediate grade, G2), and poorly differentiated (high grade, G3).

The pathology report should include these elements: tumour location, size, pathologic T and N stage (according to the Union for International Cancer Control staging manual, 7th edition, 2009), margin status, presence of lymphatic and vascular invasion, necrosis, tumour grade (based on mitotic rate per 10 hpf, or Ki-67 index per the WHO 2010 classification, or both), and immunohistochemical stains that confirm neuroendocrine differentiation, such as synaptophysin and cga if applicable.

A few biochemical tests were proposed to improve diagnosis and to facilitate follow-up: serum cga and 24-hour urinary 5-HIAA. Serum cga is a precursor of a variety of biologically active peptides that can influence tumour progression and metastasis development. The sensitivity of cga is about 63%; its specificity is 98%. It can be elevated in functioning and nonfunctioning NETs, making it helpful in NET diagnosis and monitoring.

In contrast to cga, 5-HIAA might be elevated only in functioning tumours. Serotonin produced by a functioning NET is known to be metabolized in liver, lungs, and brain into 5-HIAA; detection of 5-HIAA in 24-hour urine has 73% sensitivity and 100% specificity for a well-differentiated NET. Compared with patients having a low level of 5-HIAA, patients having a high level experience poorer prognosis and often develop valvular heart disease.

The diagnostic approach to NET also includes computed tomography, a widely available and safe modality. Computed tomography should be routinely used in the primary diagnosis of NET, in tumour assessment before hepatic artery embolization or radiofrequency ablation, in preoperative assessment, and in monitoring disease status.

Another diagnostic modality, 111In–pentetreotide scintigraphy (octreotide imaging), plays a crucial role in disease staging and monitoring. Pentetreotide, a somatostatin analog (saa) labelled with radioactive 111In, shares the somatostatin receptor–binding sites with octreotide and concentrates in tumours. It thus identifies octreotide-avid lesions throughout the body. It is not only beneficial in disease diagnosis, but also suggests a potential benefit in disease control with therapeutic doses of octreotide.

Meta-iodobenzylguanidine accumulates in gastroenterohepatic NETs; metaiodobenzylguanidine might therefore play a role in diagnosing and monitoring patients in whom octreotide imaging is negative, identifying those who could potentially benefit from therapy with radiolabelled molecules.

**What Is the Role of SSA in the Treatment of Metastatic or Unresectable Well-Differentiated Gastroenteropancreatic NET?**

- In unresectable or metastatic, progressive, well-differentiated gastroenteropancreatic NET, regular injections of saa should be considered to relieve symptoms and to prevent disease progression (level I evidence).

**Summary of Evidence**

Since the 1980s, SSA has been widely used in the treatment of patients with symptomatic NET. These analogs significantly improve disease-related symptoms and lower or normalize levels of 5-HIAA, reducing the patient’s risk of developing carcinoid heart disease. The efficacy and safety of SSA (lanreotide in extended release or depot formulations) in the treatment of patients with carcinoid syndrome was also evident in another phase III trial that was presented at the 2014 American Society of Clinical Oncology annual meeting.

The first randomized study to evaluate the antitumour effect of an SSA was the PROMID trial. Time to progression, the primary endpoint, was 15.6 months in the treated population compared with 5.9 months in the control (placebo) arm, a statistically and clinically significant result. The benefit was observed regardless of the functional status of the tumour. An overall survival (OS) benefit was not observed, probably because crossover on disease progression was allowed.

Another phase III trial to support the antiproliferative effect of SSA in non-functioning NETs was the CLARINET study, which enrolled 204 patients with well- or moderately differentiated gastroenteropancreatic NET. The primary
endpoint, progression-free survival (PFS), was 18 months in the placebo group and not reached in the experimental group at the time of the report. In both trials, the greatest benefit was observed in patients with a low hepatic tumour burden (<10%) and a resected primary.

**What Is the Role of Sunitinib and Everolimus in the Treatment of Metastatic or Unresectable NET?**
- Currently, there are data to support treatment with sunitinib or everolimus in metastatic or unresectable pancreatic NET (pNET) (level I evidence).
- The data are insufficient to recommend sunitinib or everolimus in the treatment of other NETs.
- The optimal sequencing of sunitinib and everolimus with respect to other treatment modalities has not been established (level II evidence).

**Summary of Evidence**
Various signalling pathways—such as mTOR (the mammalian target of rapamycin), vascular endothelial growth factor (VEGF) and its receptors, and platelet-derived growth factor and its receptors, among many others—are implicated in the pathogenesis of pNET. Activation of those pathways promotes tumour development and growth. In phase I and II clinical trials, as well as in the preclinical setting, the multi-targeted tyrosine kinase inhibitor sunitinib has shown activity in the treatment of pNET.

A phase III randomized placebo-controlled study that evaluated the effect of sunitinib in advanced well-differentiated pNET found that its primary endpoint—PFS—was significantly higher in the treatment arm: 11.4 months compared with 5.5 months in the placebo arm (hazard ratio (HR): 0.42; 95% confidence interval (CI): 0.26 to 0.55; p < 0.001). The objective response rate of 9.3% (compared with 0% for placebo) favoured sunitinib. The study was discontinued early because of a high number of adverse effects and deaths in the control arm.

Another phase III trial studied the effect of the mTOR inhibitor everolimus in the treatment of advanced pNET. Patients treated in the experimental arm experienced a median PFS that was improved by a factor of 2.4 compared with survival in the control arm (11 months vs. 4.6 months; HR: 0.35; 95% CI: 0.27 to 0.45; p < 0.0001). Everolimus was also associated with a significant reduction in tumour-secreted hormones and, correspondingly, functional syndromes.

The safety profiles of sunitinib and everolimus were both consistent with previously reported data. No available data support the use of one agent over the other; the decision should probably be made based on the patient’s condition and comorbidities and drug availability.

**What Is the Role of Chemotherapy in the Management of NET?**
- Chemotherapy is a viable treatment option for well-differentiated metastatic pNET (level II evidence).
- Capecitabine and temozolomide or streptozocin-based combinations can be considered.
- Consider trial referral when appropriate.
- For poorly differentiated neuroendocrine carcinoma, platinum-based chemotherapy is recommended (level II evidence).

**Summary of Evidence**
Chemotherapy is a treatment of choice for poorly differentiated neuroendocrine carcinoma with a high Ki-67 index. Historically, a combination of cisplatinum with etoposide has been used, although the response rate to that combination is about 67%, and 2-year survival is as low as 29% or less. Neuroendocrine tumours with a low Ki-67 index are often chemotherapy-resistant, with an overall response rate of 10%–16%. A streptozocin-based regimen is the most common chemotherapy in that setting, having an estimated response rate of 10%–45%, but side effects and toxicities are major factors limiting its use. In Canada, streptozocin is available only through a special-access program.

A growing body of evidence suggests that a newer combination of capecitabine with temozolomide might be beneficial in the treatment of well-differentiated NET. Results of ongoing phase II trial of capecitabine–temozolomide in the treatment of progressive well-differentiated NET were presented at the 2014 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. The overall response rate was 43%, with a complete response rate of 11%. Clinical benefit was observed in 97% of patients. The main critique of the trial was its low enrolment and tumour site heterogeneity. Further studies are warranted.

**What Is the Role for Surgery and Locoregional Treatment in Managing NET?**
- If feasible, patients should undergo primary tumour resection (level I evidence).
- Patients with metastatic disease should be referred to a multidisciplinary team to consider primary tumour and metastases resection (level II evidence).
- In unresectable disease (primary tumour, or liver, or both), locoregional therapy such as hepatic intra-arterial embolization, chemoembolization, or radiofrequency ablation could be an option (level II evidence).
- Lymphadenectomy is recommended for small-bowel tumours or primaries larger than 2 cm.
- In potentially resectable disease, surgery can include lymphadenectomy, peritoneal stripping, or liver resection.

**Summary of Evidence**
Curative surgery, if feasible, is a treatment of choice. The size of the tumour does not always correlate with its metastatic propensity; surgery should therefore involve lymphadenectomy, with clearance of all involved lymph nodes. Well-differentiated NETs are slow-growing tumours that are often metastatic on presentation. Nevertheless, patients can still experience prolonged survival with resectable metastatic disease, curative surgery is still feasible in up to 20% of patients. The resection is recommended to include primary tumour, regional lymph nodes, and resectable liver metastases. The 5-year survival rate after such extensive surgery is 61% (and can be even higher in some centres), in contrast with the reported 30% without surgery. Evidence of a benefit from surgery in patients with unresectable disease is increasing. The goal is symptom improvement, normalization or reduction of 5-HIAA levels,
and hopefully, prolongation of life. Thus, a meta-analysis of cytoreductive partial hepatectomy in patients with metastatic NET reported a 5-year survival rate of 71%45. In 86% of cases, the patient was symptom-free for 4–120 months. Results observed in two recently published trials—PROMID and CLARINET—also support a cytoreductive approach in patients with metastatic NET25,26. In the PROMID study, PFS in patients taking a SSA was 24.1 months in those having a high hepatic tumour load and not reached in those having a low hepatic load. In the CLARINET trial, the primary endpoint of time to progression for patients treated with SSA was 27.14 months in those with low-hepatic-load disease and 10.35 months in those with high-volume disease. The trend was the same in the control arms of both trials.

Other options for locoregional treatment in patients with unresectable disease are hepatic artery embolization (with or without chemotherapy) and radiofrequency ablation. Thus, in a trial of 122 patients with metastatic NET who underwent hepatic artery embolization, 82% experienced tumour regression and 12% experienced stable disease, with a median response duration of 19 months46. The effectiveness of radiofrequency ablation was suggested by recent trial in 148 patients with unresectable metastatic liver NETs47. In 185 procedures performed, a complete response was observed in 2.7%; a partial response in 60.5%; progressive disease in 4.9%; and an imaging response in 22.7%. Median survival was 70 months in the study patients.

Role of the Multidisciplinary Team in NET Management

- We recommend that NET be managed in a multidisciplinary fashion.

Summary of Evidence

Gastroenteropancreatic NETs are uncommon neoplasms that are often metastatic on presentation. Management can involve a variety of experts such as surgeons, medical and radiation oncologists, radiologists, and pathologists. A multidisciplinary approach in centres of expertise is advisable5.

MANAGEMENT OF LOCALLY ADVANCED AND METASTATIC PCC

What Is the Role of Systemic Therapy in the Management of Locally Advanced PCC?

- Systemic therapy should be considered a primary modality in the treatment of locally advanced PCC (LAPCC).
- Based on expert opinion, multiple therapeutic regimes such as gemcitabine; gemcitabine and nab-paclitaxel in combination; and a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) can be considered in the management of LAPCC (level III evidence).
- Patients with borderline resectable disease should be discussed at multidisciplinary rounds or referred to trials (or both).

Summary of Evidence

The bulk of the evidence on the treatment of LAPCC was extrapolated from trials on metastatic PCC (mPCC). Historically, single-agent gemcitabine has been a standard of care in this clinical setting48. It was shown to be superior to 5-fluorouracil in terms of OS (5.65 months vs. 4.41 months in favour of gemcitabine) and to provide clinical benefits such as improved performance status, pain measures, and use of analgesics, and less weight loss.

The introduction of FOLFIRINOX in 2010 was a revolutionary event in GI medical oncology, with a reported improvement in OS from 5.65 months with gemcitabine to 11.1 months with the new combination49. However, data in the LAPCC population are limited. In a pilot study of neoadjuvant FOLFIRINOX in 18 patients with unresectable or borderline resectable LAPCC, 7 were converted to resectability, with 5 receiving an R0 resection, and 1 receiving an R1 resection. One patient remained unresectable. Of the 11 patients who remained unresectable after FOLFIRINOX, 3 were converted to resectability after treatment with chemoradiation50. Further trials are warranted.

Another effective combination (gemcitabine and nab-paclitaxel) was also investigated in the setting of metastatic disease. Single-agent gemcitabine served as the control arm51,52. The reported median OS was 8.7 months in the investigational arm and 6.6 months in the control arm. Secondary endpoints such as PFS, overall response rate, and 1-year survival were significantly improved.

Evidence for the role of neoadjuvant therapy in the management of borderline resectable PCC is limited. Most trials were phase II investigations with small numbers of patients and varying primary endpoints53. However, a subset of patients who were converted to resectability after neoadjuvant therapy53,54, and so management of patients with borderline-resectable PCC should be discussed at multidisciplinary tumour boards. Trial referral is advisable when appropriate53.

Role of Chemoradiation the Management of LAPCC

- Recent trials failed to support the superiority of chemoradiation over chemotherapy alone in LAPCC (level III evidence).
- Chemoradiation can be considered in selected patient populations after discussion within a multidisciplinary team or in a trial setting.

Summary of Evidence

The role of chemoradiation in the management of LAPCC has been ambiguous. Evidence for the superiority of chemoradiation over chemotherapy alone is limited. Data that support the chemoradiation approach came from trials that used older chemotherapy regimens55, and local treatment failure was reported to be frequent56. Recent trials using conventional radiation therapy or stereotactic radiation with chemotherapy are small and report improved local control57–60. However, treatment failure is associated with distant metastatic disease. A regimen of chemotherapy for 3–6 months followed by radiation might exclude patients with disease progression from the radiation cohort56,57. In selected patients, chemoradiation can be considered after discussion at a multidisciplinary tumour board or in clinical trials when appropriate.

Management of mPCC

- In fit patients, FOLFIRINOX or combination therapy with gemcitabine–nab-paclitaxel can be recommended as first-line therapy (level I evidence).
Summary of Evidence

Metastatic pancreatic cancer carries a grim prognosis. The 5-year overall survival (os) is just 6%49. Gemcitabine has been a treatment of choice since a randomized trial comparing gemcitabine with infusional 5-fluorouracil reported a modest improvement in median os (1-year survival: 18% with gemcitabine vs. 2% with 5-fluorouracil; p = 0.003) and alleviation of disease-related symptoms48, with a manageable toxicity profile. Multiple trials investigating various gemcitabine-based combinations in pancreatic cancer failed to show an improvement in os that was statistically and clinically meaningful41–63.

For many years, single-agent gemcitabine was the only available option in the metastatic setting. Then, a multicentre phase III trial comparing folfirinox with gemcitabine was presented at the 2010 American Society of Clinical Oncology annual meeting49. The reported os—11.1 months with folfirinox and 6.8 months with gemcitabine—favoured the investigational arm (HR: 0.57; 95% CI: 0.45 to 0.73; p < 0.001). Progression-free survival was also significantly improved in the folfirinox arm: 6.4 months compared with 3.3 months. However, folfirinox was associated with more toxicity: 5.4% of patients receiving it experienced febrile neutropenia. On the basis of that trial, folfirinox was adopted as first-line treatment for pancreatic cancer in fit patients. In clinical practice, many patients require dose modifications for one or more of the agents. Data concerning the effect of dose modification on os are controversial43.

Another phase III trial studied gemcitabine in combination with nab-paclitaxel in patients with pancreatic cancer who were chemotherapy-naïve and had a Karnofsky performance status of 70% or better51. Median os was 8.5 months, compared with 6.7 months in the control group (HR: 0.72; 95% CI: 0.62 to 0.83; p < 0.001); pfs in investigational arm was also improved. The combination of agents was more toxic than gemcitabine alone, with the most common toxicities being neutropenia (38% vs. 27%), fatigue (17% vs. 1%), and neuropathy (17% vs. 1%). Gemcitabine–nab-paclitaxel is considered a standard first-line treatment in the setting of pancreatic cancer.

Multiple phase I/II trials in pancreatic cancer have investigated new anticancer agents alone or in combination with chemotherapy. Trial participation in appropriately selected patients is encouraged.

Up to 5%–10% of patients with pancreatic cancer report a family history that suggests a role of heritable genetic factors in the development of the disease65. The reasons for most familial clustering are still unknown. However, a few important pancreatic cancer genes such as BRCA2 and PALB2 have been identified. Patients harbouring mutations often are resistant to conventional treatment, but can respond to agents proven to work in particular settings66,67. Thus, a patient with a germline BRCA2 mutation and associated pancreatic cancer treated with the poly(ADP–ribose) polymerase 1 inhibitor, but further studies are required.

TREATMENT OF METASTATIC CRC WITH EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITOR: TESTING BEYOND KRAS

What Constitutes Expanded RAS Wild-Type Analysis?

- Traditional KRAS mutation testing includes mutations in exon 2, codons 12 and 13, and accounts for 40% of the population68,69.
- Expanded RAS mutations account for approximately 20% (15%–28%) of the additional mutations68,70–73.
- Expanded RAS mutation testing is defined to include testing of KRAS and NRAS exons 2, 3, and 4.
- The issue of BRAF mutation as a predictive or prognostic biomarker was not formally reviewed.

Who Should Receive Expanded RAS Testing?

- Extended RAS wild-type (wt) status correlates with significant improvements in pfs and os when patients with metastatic colorectal cancer (mCRC) are treated with epidermal growth factor receptor (EGFR) inhibitors in the first-line, second-line, and third-line settings70,72,74,75.
- For initial treatment planning purposes, all patients should, upon diagnosis of mCRC, be tested in a timely manner for extended RAS mutations.

How Does the Result of Expanded RAS Testing Affect Choice of Therapy?

- Patients without extended RAS mutations might experience pfs and os benefits with the use of EGFR inhibitors68.
- Patients with RAS mutations show no benefit with EGFR inhibitors (alone or in combination with chemotherapy); in fact, treatment with EGFR inhibitor might have a deleterious effect on cancer outcomes (pfs or os)68,74.
- No EGFR inhibitor should be initiated in patients proved to have any RAS mutation; use of such an inhibitor can expose patients to unnecessary harm and are an inappropriate use of health care resources.

Summary of the Evidence

Colorectal cancer is the third most commonly diagnosed malignancy and the second leading cause of cancer death in Canada76. Prognosis for patients with metastatic disease has steadily improved, with advances in the therapeutic strategies of chemotherapy and biologic therapy such as VEGF and EGFR inhibitors. An established predictive biomarker of resistance to treatment with EGFR inhibitors is the presence of KRAS mutation, which leads to constitutive activation of the Ras–Raf–MEK signalling pathway77.
Conventional KRAS mutation testing involves assessment of codons 12 and 13 (exon 2), with mutations noted in approximately 36%–40% of patients. More recently, genomic analyses have uncovered further mutations in KRAS, NRAS, and BRAF that might also play a role as prognostic or predictive biomarkers, leading to extended RAS mutation testing involving KRAS exons 3 and 4 and NRAS exons 2, 3, and 4. Approximately 20% of tumours previously considered KRAS wt harbour an extended RAS mutation. In a systematic review and meta-analysis of nine randomized controlled trials evaluating EGFR inhibitor in tumours tested for all RAS mutations, benefits in both pfs and os (hr: 0.62; 95% ci: 0.5 to 0.76) and os (hr: 0.87; 95% ci: 0.77 to 0.99) were noted when EGFR inhibitor was used in RAS wt tumours, regardless of the inhibitor used (cetuximab or panitumumab) or the chemotherapy backbone (iri-otecan- or oxaliplatin-based). Conversely, patients with RAS mutations experienced demonstrably shorter pfs and os when treated with EGFR inhibitor plus chemotherapy than with chemotherapy alone. For example, in the updated analysis of the PRIME study, patients positive for a RAS mutation experienced a pfs of 7.3 months (95% ci: 6.3 to 7.9 months) on FOLFIRI (leucovorin–fluorouracil–oxaliplatin) plus panitumumab compared with 8.7 months (95% ci: 7.6 to 9.4 months) on FOLFOX4 alone.

**EGFR INHIBITORS IN THE FIRST-LINE TREATMENT OF mCRC**

**What Is the Role of EGFR Inhibitor in the Treatment of mCRC in the First-Line Setting?**
- Chemotherapy plus bevacizumab remains a standard palliative treatment in the first line for mCRC (level i evidence).
- Chemotherapy plus EGFR inhibitor is an option for unresectable mCRC in the first line setting in patients with known RAS wt status (level i evidence).
- If considering double therapy (chemotherapy plus biologic therapy), then, based on the largest randomized controlled trial to date, chemotherapy plus bevacizumab remains the preferred regimen (level i evidence).

**Summary of the Evidence**

The prognosis for patients with mCRC has steadily improved with the addition of biologics to standard chemotherapy. The addition of bevacizumab, a monoclonal antibody against VEGF, to first-line chemotherapy has improved both pfs and os in irinotecan-based and oxaliplatin-based chemotherapies alike. An EGFR inhibitor in combination with chemotherapy has also been investigated for the first-line treatment of mCRC, with some studies hinting at its superiority over VEGF inhibitor plus chemotherapy. For instance, the FIRE-3 trial demonstrated a median os benefit of 3.7 months for cetuximab plus FOLFIRI (leucovorin–fluorouracil–iri-otecan) compared with bevacizumab plus FOLFIRI (hr: 0.77; 95% ci: 0.62 to 0.96; p = 0.017) despite the former combination not meeting its primary endpoint of objective response benefit. The PEAK study, a randomized phase II trial comparing panitumumab plus mFOLFOX6 with bevacizumab plus mFOLFOX6, also showed an os benefit for the panitumumab arm (hr: 0.62; 95% ci: 0.44 to 0.89; p = 0.009), without meeting its primary objective of a pfs benefit in the intention-to-treat KRAS exon 2 wt group. However, in the largest study that was best powered for os, bevacizumab plus chemotherapy (FOLFIRI or FOLFOX) was compared with cetuximab plus chemotherapy in untreated KRAS exon 2 wt mCRC patients, demonstrating equivalent os in the treatment arms (hr: 0.92; 95% ci: 0.78 to 1.09; p = 0.34). Furthermore, updated results presented at the European Society for Medical Oncology 2014 annual meeting did not reveal an os benefit of cetuximab plus chemotherapy compared with bevacizumab plus chemotherapy in the expanded all-RAS wt population.

**SCREENING FOR CRC**

**What Is the Recommendation for CRC Screening in the General Population?**
- We recommend population-based CRC screening with the fecal occult blood test (FOBT), the fecal immunochemical test (FIT), or flexible sigmoidoscopy for asymptomatic patients 50–74 years of age.
- Colonoscopy-based screening has no level i evidence for mortality benefit; furthermore, it is associated with issues of test access and quality.
- Colonoscopy remains the preferred follow-up test after a positive screen and should be completed within 8 weeks.

**What Is the Recommendation for Screening Individuals at Increased Risk of CRC?**
- To elucidate possible hereditary cancer syndromes or a genetic predisposition to CRC, we recommend that a full and appropriate family history be recorded for all patients. Patients with a positive family history should be referred for genetic evaluation.
- We endorse the guideline created by the U.S. Multi-Society Task Force on Colorectal Cancer for the screening and management of hereditary nonpolyposis CRC (HNPCC).

**Summary of Evidence**

Screening for CRC reduces the risk of death from CRC, with early detection and removal of pre-malignant or localized cancers. Provincial CRC screening programs have therefore been established across Canada. A participation target rate exceeding 60% has been established as an indicator of screening program quality; however, participation rates in provincial screening programs remain suboptimal (<40%). Beyond poor participation, other challenges in CRC screening include inconsistencies with respect to test choice, poor follow-up of positive tests, and inappropriate use of screening tests.

Screening tests for CRC include the FOBT, the FIT, flexible sigmoidoscopy, and colonoscopy. Biennial use of the FOBT has been reported to reduce CRC mortality by approximately 15%. Compared with the FOBT, the FIT, which detects globin rather than heme, benefits from higher rates of participation, greater sensitivity to GI bleeding, greater specificity for lower GI bleeds, and greater sensitivity to advanced adenomas. In addition, FIT has been noted to have CRC detection rates similar to those with colonoscopy. On systematic

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review, in which it was compared with no screening, screening by flexible sigmoidoscopy, which is limited to the lower half of the colon but does not require sedation or complete bowel preparation, was associated with lowered crc mortality (relative risk: 0.72; 95% ci: 0.65 to 0.79)96. Evidence of crc incidence and mortality reduction after colonoscopy screening is limited to observational and case–control studies. One such population-based case–control study noted that colonoscopy in the preceding 10 years was associated with a 77% lower risk of crc development97. Another case–control study demonstrated that complete colonoscopy was strongly associated with fewer deaths from left-sided crc only (adjusted conditional odds ratio: 0.33; 95% ci: 0.28 to 0.39)98. Thus, because of its questionable ability to detect right-sided tumours (as well as other issues surrounding colonoscopy access, quality, and safety), colonoscopy is not universally recommended as a screening tool98,99. Nevertheless, colonoscopy is recommended as a follow-up diagnostic test after positive screening test results91.

Fewer than 10% of colorectal cancers arise in people with hereditary syndromes (hnPCC), the most prevalent of which is Lynch syndrome100. Patients with hnPCC are at higher risk of developing crc and also cancers of the endometrium, ovary, small bowel, stomach, hepatobiliary organs, and renal pelvis or ureter101. The U.S. Multi-Society Task Force on Colorectal Cancer recently set out guidelines for the evaluation and management of Lynch syndrome, including crc screening guidelines90. Accordingly, colonoscopy screening is recommended in at-risk individuals every 1–2 years beginning at 20–25 years of age or at 2–5 years less than the youngest age at diagnosis of crc in the family if that diagnosis came before age 25. The guidelines further recommend that colonoscopies should start at 30 years of age in families with MSH6 mutations and at 35 years of age in those with PMS2 mutations; carriers of an MMR mutation should receive annual colonoscopy screening.

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CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’ s policy on disclosing conflicts of interest, and we declare that we have none.

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