CURRENT ONCOLOGY

PRACTICE GUIDELINE

Eastern Canadian Gastrointestinal Cancer Consensus Conference 2014

E. Tsvetkova MD,*[a] S. Sud MD,*[a] N. Aucoin MD,† J. Biagi MD,‡ R. Burkes MD,§ B. Samson MD,|| S. Brule MD,* C. Cripps MD,* B. Colwell MD,# C. Falkson MD,‡ M. Dorreen MD,# R. Goel MD,* F. Halwani MD,* J. Maroun MD,* N. Michaud MD,** M. Tehfe MD,†† M. Thirlwell MD,‡‡ M. Vickers MD,* and T. Asmis MD*

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

Curr Oncol. 2015 Aug;22(4):e305-e315 www.current-oncology.com

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 evidence[1]. 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)

[a] These authors contributed equally to the present work.

Correspondence to: Elena Tsvetkova, The Ottawa Hospital Cancer Centre, Room C2433, 501 Smyth Road, Box 900, Ottawa, Ontario K1H 8L6. E-mail: dmtrs03101984@gmail.com **DOI:** http://dx.doi.org/10.3747/co.22.2603

- 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

Nathalie Aucoin	Medical oncologist	Hôpital de la Cité-de-la-Santé, Laval, QC
Bruce Colwell	Medical oncologist	Dalhousie University, Halifax, NS
Stephanie Brule	Medical oncologist	University of Ottawa, Ottawa, ON
Ronald Burkes	Medical oncologist	Mount Sinai Hospital, Toronto, ON
Catherine Dube	Gastroenterologist	The Ottawa Hospital, Ottawa, ON
Celia Marginean	Pathologist	The Ottawa Hospital, Ottawa, ON
Christine Cripps	Medical oncologist	University of Ottawa, Ottawa, ON
Conrad Falkson	Radiation oncologist	Queen's University, Kingston, ON
Richard Dalfen	Medical oncologist	St. Mary's Hospital, Montreal, QC
Elena Tsvetkova	Medical oncologist	The Ottawa Hospital Cancer Centre, Ottawa, ON
Mark Dorreen	Medical oncologist	Dalhousie University, Halifax, NS
Rakesh Goel	Medical oncologist	The Ottawa Hospital, Ottawa, ON
Fawaz Halwani	Pathologist	Eastern Ontario Regional Laboratory Association, Ottawa, ON
Jim Biagi	Medical oncologist	Queen's University, Kingston, ON
Marion L'Espérance	Surgeon	Centre de Santé et de Services sociaux de Sept-Iles, Sept-Iles, QC
Lucas Sideris	Surgeon	Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, QC
Benoit Samson	Medical oncologist	Le Centre intégré de cancérologie de la Montérégie, Hôpital Charles-LeMoyne, Longueuil, QC
Malcolm Moore	Medical oncologist	University Health Network, Princess Margaret Hospital, Toronto, ON
Jean Maroun	Medical oncologist	The Ottawa Hospital Cancer Centre, Ottawa, ON
Michael Thirlwell	Medical oncologist	McGill University Health Centre, Montreal, QC
Nathalie Michaud	Surgeon	Centre de Santé et de Services sociaux de Sept-Iles, Sept-Iles, QC
Nazik Hammad	Medical oncologist	Queen's University, Kingston, ON
Marie-Helene Nepveu	Gastroenterologist	Hôpital de LaSalle, LaSalle, QC
Nadège Perrin	Surgeon	Centre de Santé et de Services sociaux de Sept-Iles, Sept-Iles, QC
Berry Scott	Medical oncologist	Sunnybrook Odette Cancer Centre, Toronto, ON
Scot Dowden	Medical oncologist	Tom Baker Cancer Centre, Calgary, AB
Shelly Sud	Medical oncologist	The Ottawa Hospital Cancer Centre, Ottawa, ON
Mustapha Tehfe	Medical oncologist	Centre hospitalier de l'Université de Montréal, Montreal, QC
Tim Asmis	Medical oncologist	The Ottawa Hospital Cancer Centre, Ottawa, ON
Michael Vickers	Medical oncologist	University of Ottawa, Ottawa, ON

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[2]. The most common sites of origin are the GI tract (64%) and bronchopulmonary system (28%)[3]. In Canada, NETs represent about 0.25% of all oncology cases[4,5], with the incidence showing a rising trend since the mid-1980s[4]. 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[6].

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 biohistochemical differences. In 1980, WHO adopted classifications that subdivided tumours based on granulostaining technique (for example, gastrin-cell carcinoid, enterochromaffin-cell carcinoid, and so on)[7,8]. 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)[9].

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[10,11].

A few biochemical test were proposed to improve diagnosis and to facilitate follow-up: serum CgA and 24-hour urinary 5-HIAA[5]. Serum CgA is a precursor of a variety of biologically active peptides that can influence tumour progression and metastasis development[12]. 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[13,14].

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[5].

Another diagnostic modality, ^{111}In–pentetreotide scintigraphy (octreotide imaging), plays a crucial role in disease staging and monitoring[5]. Pentetreotide, a somatostatin analog (SSA) labelled with radioactive ^{111}In, shares the somatostatin receptor–binding sites with octreotide and concentrates in tumours[15]. 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[16].

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[17,18].

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 SSA should be considered to relieve symptoms and to prevent disease progression (level I evidence).

Summary of Evidence

Since the 1980s, SSAs have 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[5,19–23]. 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 (ELECT) that was presented at the 2014 American Society of Clinical Oncology annual meeting[24].

The first randomized study to evaluate the antitumour effect of an SSA was the PROMID trial[25]. 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[26]. 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 III 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 NET[24,27]. Activation of those pathways promotes tumour development and growth[28]. 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; $p < 0.001$)][28]. 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[29]. 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[18,30]. Neuroendocrine tumours with a low Ki-67 index are often chemotherapy-resistant, with an overall response rate of 10%–16%[31]. A streptozocin-based regimen is the most common chemotherapy in that setting, having an estimated response rate of 10%–45%[32,33], 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[34]. The reported 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 III evidence).
- Patients with metastatic disease should be referred to a multidisciplinary team to consider primary tumour and metastases resection (level III 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[35]. 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[36–39].

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[36,40,41]. 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[42–44].

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 NET[25,26]. 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 months[46]. The effectiveness of radiofrequency ablation was suggested by recent trial in 148 patients with unresectable metastatic liver NETS[47]. 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 advisable[5].

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 regimens 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 setting[48]. 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 combination[49]. 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 chemoradiation[50]. 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 arm[51,52]. 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 endpoints[53]. However, a subset patients were converted to resectability after neoadjuvant therapy[53,54], and so management of patients with borderline-resectable PCC should be discussed at multidisciplinary tumour boards. Trial referral is advisable when appropriate[53].

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 regimens[55], and local treatment failure was reported to be frequent[56]. Recent trials using conventional radiation therapy or stereotactic radiation with chemotherapy are small and report improved local control[57–60]. 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 cohort[56,57]. 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).

- Dose modification and supportive care during FOLFIRINOX treatment are at the treating physician's discretion.
- For patients with a borderline performance status, discussion of gemcitabine or best supportive care can be appropriate.
- Trial participation in appropriately selected patients is encouraged.
- There is evidence to support the use of second-line therapy in the management of MPCC, but the evidence at this time is insufficient to specify a regimen.
- In selected patients with a genetic predisposition, consideration of individualized treatment might be appropriate (level III evidence). That treatment could include a platinum-based regimen or poly(ADP–ribose) polymerase 1 inhibitor, but further studies are required.

Summary of Evidence

Metastatic PCC carries a grim prognosis. The 5-year 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 symptoms[48], with a manageable toxicity profile. Multiple trials investigating various gemcitabine-based combinations in MPCC failed to show an improvement in OS that was statistically and clinically meaningful[61–63].

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 meeting[49]. 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 MPCC 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 controversial[64].

Another phase III trial studied gemcitabine in combination with nab-paclitaxel in patients with MPCC who were chemotherapy-naïve and had a Karnofsky performance status of 70% or better[51]. 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 MPCC.

Multiple phase I/II trials in MPCC 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 PCC report a family history that suggests a role of heritable genetic factors in the development of the disease[65]. The reasons for most familial clustering are still unknown. However, a few important PCC 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 settings[66,67]. Thus, a patient with a germline *BRCA2* mutation and associated PCC treated with the poly(ADP–ribose) polymerase inhibitor iniparib demonstrated a complete pathologic response. That case highlights the potential for individualized treatment in selected patients with a genetic predisposition to PCC.

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 population[68,69].
- Expanded *RAS* mutations account for approximately 20% (15%–28%) of the additional mutations[68,70–73].
- 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 CRC (MCRC) are treated with epidermal growth factor receptor (EGFR) inhibitors in the first-line, second-line, and third-line settings[70,72,74,75].
- 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 inhibitors[68].
- 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 Canada[76]. 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 pathway[77].

Conventional *KRAS* mutation testing involves assessment of codons 12 and 13 (exon 2), with mutations noted in approximately 36%–40% of patients[78,79]. More recently, genomic analyses have uncovered further mutations in *KRAS, NRAS,* and *BRAF* that might also play a role as prognostic or predictive biomarkers[80], 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[72]. 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 (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 (irinotecan- or oxaliplatin-based)[72]. Conversely, patients with *RAS* mutations experienced demonstrably shorter PFS and OS when treated with EGFR inhibitor plus chemotherapy than with chemotherapy alone[68,74]. 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 FOLFOX4 (leucovorin–fluorouracil–oxaliplatin) plus panitumumab compared with 8.7 months (95% CI: 7.6 to 9.4 months) on FOLFOX4 alone[68].

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[81–83] (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[78,84,85] (level I evidence).
- If considering doublet therapy (chemotherapy plus biologic therapy), then, based on the largest randomized controlled trial to date[86], 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[81] and oxaliplatin-based[83] 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–irinotecan) compared with bevacizumab plus FOLFIRI (HR: 0.77; 95% CI: 0.62 to 0.96; $p = 0.017$)[87] 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[88]. 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; $p = 0.34$)[86]. 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[73].

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[89].

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)[90].

Summary of Evidence

Screening for CRC reduces the risk of death from CRC, with early detection and removal of pre-malignant or localized cancers[91]. 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%)[92]. 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%[93]. Compared with the FOBT, the FIT, which detects globin rather than heme, benefits from higher rates of participation[94], greater sensitivity to GI bleeding[93], greater specificity for lower GI bleeds, and greater sensitivity to advanced adenomas[94]. In addition, FIT has been noted to have CRC detection rates similar to those with colonoscopy[95]. On systematic

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 development[97]. 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 tool[98,99]. Nevertheless, colonoscopy is recommended as a follow-up diagnostic test after positive screening test results[91].

Fewer than 10% of colorectal cancers arise in people with hereditary syndromes (HNPCC), the most prevalent of which is Lynch syndrome[100]. 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 ureter[101]. 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 guidelines[90]. 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.

ACKNOWLEDGMENTS

The Planning Committee for the 2014 EC5 thanks the following organizations for their generosity in sponsoring the conference: Amgen Canada, Bayer Canada, Bristol–Myers Squibb Canada, Celgene, Lilly, Novartis, Pfizer, Roche, and Sanofi Oncology.

The committee also acknowledges these EC5 attendees for their assistance in creating the present consensus statement: Richard Dalfen (St. Mary's Hospital, Montreal, QC), Marion L'Espérance (Centre de Santé et de Services sociaux de Sept-Îles, Sept-Îles, QC), Nadege Perrin (Centre de Santé et de Services sociaux de Sept-Îles, Sept-Îles, QC), and Marie-Helene Nepveu (Hôpital de la Cité-de-la-Santé de Laval, Montreal, QC).

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.

AUTHOR AFFILIATIONS

*The Ottawa Hospital Cancer Centre, Ottawa, ON; †Hôpital de la Cité-de-la-Santé de Laval, Laval, QC; ‡Queen's University, Kingston, ON; §Mount Sinai Hospital, Toronto, ON; ‖Monteregie Cancer Centre, Charles-LeMoyne Hospital, Longueil, QC; #Dalhousie University, Halifax, NS; **Centre de Santé et de Services sociaux de Sept-Îles, Sept-Îles, QC; ††Centre hospitalier de l'Université de Montréal, Montreal, QC; ‡‡McGill University Health Centre, Montreal, QC.

REFERENCES

1. Palda VA, Guise JM, Wathen CN, on behalf of the Canadian Task Force on Preventive Health Care. Interventions to promote breast-feeding: applying the evidence in clinical practice. Definitions of levels of evidence and grades of recommendations of the Canadian Task Force on Preventive Health Care [e-Appendix 1]. *CMAJ* 2004;170:976-8. [Available online at: http://www.cmaj.ca/content/suppl/2004/03/15/170.6.976.DC1/palda_appendix.pdf; cited 13 December 2014]
2. Rindi G, Kloppel G, Alhman H, *et al.* on behalf of the Frascati Consensus Conference participants and the European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;449:395–401.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934–59.
4. Maroun J, Kocha W, Kvols L, *et al.* Guidelines for the diagnosis and management of carcinoid tumours. Part 1: the gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. *Curr Oncol* 2006;13:67–76.
5. Kocha W, Maroun J, Kennecke H, *et al.* Consensus recommendations for the diagnosis and management of well-differentiated gastroenterohepatic neuroendocrine tumours: a revised statement from a Canadian National Expert Group. *Curr Oncol* 2010;17:49–64.
6. Modlin IM, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol* 2004;99:23–32.
7. Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet* 1963;1:238–9.
8. Capella C, Heitz PU, Hofler H, Solcia E, Kloppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch* 1995;425:547–60.
9. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010;39:707–12.
10. Rindi G, Klöppel G, Couvelard A, *et al.* TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007;451:757–62.
11. Klimstra DS, Modlin IR, Adsay NV, *et al.* Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol* 2010;34:300–13.
12. Bajetta E, Ferrari L, Martinetti A, *et al.* Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. *Cancer* 1999;86:858–65.
13. Robiolio PA, Rigolin VH, Wilson JS, *et al.* Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation* 1995;92:790–5.
14. Denney WD, Kemp WE Jr, Anthony LB, Oates JA, Byrd BF 3rd. Echocardiographic and biochemical evaluation of the development and progression of carcinoid heart disease. *J Am Coll Cardiol* 1998;32:1017–22.
15. Reubi JC. Somatostatin and other peptide receptors as tools for tumor diagnosis and treatment. *Neuroendocrinology* 2004;80(suppl 1):51–6.
16. Kaltsas G, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. *Eur J Endocrinol* 2004;151:15–27.
17. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 2004;25:458–511.

18. Oberg K, Eriksson B. Nuclear medicine in the detection, staging and treatment of gastrointestinal carcinoid tumours. *Best Pract Res Clin Endocrinol Metab* 2005;19:265–76.
19. de Herder WW. Tumours of the midgut (jejunum, ileum and ascending colon, including carcinoid syndrome). *Best Pract Res Clin Gastroenterol* 2005;19:705–15.
20. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid heart disease. *Circulation* 2007;116:2860–5.
21. Gustafsson BI, Hauso O, Drozdov I, Kidd M, Modlin IM. Carcinoid heart disease. *Int J Cardiol* 2008;129:318–24.
22. Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. *Curr Med Res Opin* 2009;25:2989–99.
23. Rubin J, Ajani J, Schirmer W, *et al.* Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol* 1999;17:600–6.
24. Turner HE, Harris AL, Melmed S, Wass JA. Angiogenesis in endocrine tumors. *Endocr Rev* 2003;24:600–32.
25. Rinke A, Muller HH, Schade-Brittinger C, *et al.* on behalf of the PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27:4656–63.
26. Caplin ME, Pavel M, Cwikla JB, *et al.* on behalf of the CLARINET investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–33.
27. Chaudhry A, Papanicolaou V, Oberg K, Heldin CH, Funa K. Expression of platelet-derived growth factor and its receptors in neuroendocrine tumors of the digestive system. *Cancer Res* 1992;52:1006–12.
28. Raymond E, Dahan L, Raoul JL, *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501–13.
29. Yao JC, Phan AT, Jehl V, Shah G, Meric-Bernstam F. Everolimus in advanced pancreatic neuroendocrine tumors: the clinical experience. *Cancer Res* 2013;73:1449–53.
30. Plockinger U, Rindi G, Arnold R, *et al.* Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004;80:394–424.
31. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG on behalf of the Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol* 2005;23:4897–904.
32. Vilar E, Salazar R, Perez-Garcia J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. *Endocr Relat Cancer* 2007;14:221–32.
33. Jensen RT, Delle Fave G. Promising advances in the treatment of malignant pancreatic endocrine tumors. *N Engl J Med* 2011;364:564–5.
34. Fine RL, Gulati AP, Tsushima D, *et al.* Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors [abstract 179]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/122616-143; cited 30 May 2015]
35. Eriksson B, Kloppel G, Krenning E, *et al.* on behalf of the Frascati Consensus Conference participants. Consensus guidelines for the management of patients with digestive neuroendocrine tumors—well-differentiated jejunal–ileal tumor/carcinoma. *Neuroendocrinology* 2008;87:8–19.
36. Ahlman H, Wangberg B, Jansson S, *et al.* Interventional treatment of gastrointestinal neuroendocrine tumours. *Digestion* 2000;62(suppl 1):59–68.
37. Makridis C, Oberg K, Juhlin C, *et al.* Surgical treatment of mid-gut carcinoid tumors. *World J Surg* 1990;14:377–83.
38. Norton JA. Surgical management of carcinoid tumors: role of debulking and surgery for patients with advanced disease. *Digestion* 1994;55(suppl 3):98–103.
39. Goede AC, Winslet MC. Surgery for carcinoid tumours of the lower gastrointestinal tract. *Colorectal Dis* 2003;5:123–8.
40. Frilling A, Rogiers X, Malago M, Liedke OM, Kaun M, Broelsch CE. Treatment of liver metastases in patients with neuroendocrine tumors. *Langenbecks Arch Surg* 1998;383:62–70.
41. Lehnert T, Knaebel HP. Diagnosis and therapy of liver metastases of neuroendocrine tumors [German]. *Chirurg* 1997;68:122–31.
42. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003;197:29–37.
43. Chamberlain RS, Canes D, Brown KT, *et al.* Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg* 2000;190:432–45.
44. Norton JA, Warren RS, Kelly MG, Zuraek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery* 2003;134:1057–63.
45. Que FG, Sarmiento JM, Nagorney DM. Hepatic surgery for metastatic gastrointestinal neuroendocrine tumors. *Adv Exp Med Biol* 2006;574:43–56.
46. Bloomston M, Al-Saif O, Klemanski D, *et al.* Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. *J Gastrointest Surg* 2007;11:264–71.
47. Kennedy AS, Dezarn WA, McNeillie P, *et al.* Radioembolization for unresectable neuroendocrine hepatic metastases using resin ^{90}Y–microspheres: early results in 148 patients. *Am J Clin Oncol* 2008;31:271–9.
48. Burris HA 3rd, Moore MJ, Andersen J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
49. Conroy T, Desseigne F, Ychou M, *et al.* on behalf of the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
50. Hosein PJ, Macintyre J, Kawamura C, *et al.* A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 2012;12:199.
51. Von Hoff DD, Ervin T, Arena FP, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703.
52. Goldstein D, El Maraghi RH, Hammel P, *et al.* Updated survival from a randomized phase III trial (MPACT) of nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients (pts) with metastatic adenocarcinoma of the pancreas [abstract 178^]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/123211-143; cited 30 May 2015]
53. Tsvetkova EV, Asmis TR. Role of neoadjuvant therapy in the management of pancreatic cancer: is the era of biomarker-directed therapy here? *Curr Oncol* 2014;21:e650–7.
54. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
55. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy

plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988;80:751–5.
56. Wilkowski R, Boeck S, Ostermaier S, *et al.* Chemoradiotherapy with concurrent gemcitabine and cisplatin with or without sequential chemotherapy with gemcitabine/cisplatin vs chemoradiotherapy with concurrent 5-fluorouracil in patients with locally advanced pancreatic cancer—a multi-centre randomised phase II study. *Br J Cancer* 2009;101:1853–9.
57. Gillmore R, Laurence V, Raouf S, *et al.* Chemoradiotherapy with or without induction chemotherapy for locally advanced pancreatic cancer: a UK multi-institutional experience. *Clin Oncol (R Coll Radiol)* 2010;22:564–9.
58. Schellenberg D, Kim J, Christman-Skieller C, *et al.* Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011;81:181–8.
59. Mahadevan A, Jain S, Goldstein M, *et al.* Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:735–42.
60. Schellenberg D, Goodman KA, Lee F, *et al.* Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2008;72:678–86.
61. Moore MJ, Goldstein D, Hamm J, *et al.* on behalf of the NCIC Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960–6.
62. Poplin E, Feng Y, Berlin J, *et al.* Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:3778–85.
63. Colucci G, Labianca R, Di Costanzo F, *et al.* Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010;28:1645–51.
64. Maroun JA, Ko Y, Ghafoor A, *et al.* Standard clinical practice of FOLFIRINOX (FFX) in advanced/metastatic pancreatic cancer (PC) patients: a Canadian retrospective registry [abstract 702P]. *Ann Oncol* 2014;25(suppl 4):iv210–53. [Available online at: http://oncologypro.esmo.org/Meeting-Resources/ESMO-2014/Gastrointestinal-Tumours-Non-Colorectal/Standard-clinical-practice-of-FOLFIRINOX-FFX-in-advanced-metastatic-pancreatic-cancer-PC-Patients-A-Canadian-retrospective-registry; cited 30 May 2015]
65. Klein AP. Genetic susceptibility to pancreatic cancer. *Mol Carcinog* 2012;51:14–24.
66. Fogelman DR, Wolff RA, Kopetz S, *et al.* Evidence for the efficacy of iniparib, a PARP-1 inhibitor, in *BRCA2*-associated pancreatic cancer. *Anticancer Res* 2011;31:1417–20.
67. Yuan K, Sun Y, Zhou T, McDonald J, Chen Y. PARP-1 regulates resistance of pancreatic cancer to TRAIL therapy. *Clin Cancer Res* 2013;19:4750–9.
68. Douillard JY, Oliner KS, Siena S, *et al.* Panitumumab–FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med* 2013;369:1023–34.
69. Ciardiello F, van Krieken H, Duecker K, *et al.* Outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer randomized to FOLFIRI with or without cetuximab as first-line treatment [abstract O-0020]. *Ann Oncol* 2014;25(suppl 2):.
70. Peeters M, Oliner KS, Price TJ, *et al.* Analysis of *KRAS*/*NRAS* mutations in phase 3 study 20050181 of panitumumab (pmab) plus FOLFIRI versus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) [abstract LBA387]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/122548-143; cited 24 May 2015]
71. Stintzing S, Jung A, Rossius L, *et al.* Analysis of *KRAS*/*NRAS* and *BRAF* mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) *KRAS* (exon 2) metastatic colorectal cancer (mCRC) patients [abstract 17]. *Eur J Cancer* 2013;49(suppl 3):.
72. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS. Extended *RAS* mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol* 2015;26:13–21.
73. Lenz H, Niedzwiecki D, Innocenti F, *et al.* CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded *RAS* analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC) [abstract 501O]. *Ann Oncol* 2014;25(suppl 4):.
74. Bokemeyer C, Bondarenko I, Hartmann JT, *et al.* Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011;22:1535–46.
75. Patterson SD, Peeters M, Siena S, *et al.* Comprehensive analysis of *KRAS* and *NRAS* mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408) [abstract 3617]. *J Clin Oncol* 2013;31:. [Available online at: http://meetinglibrary.asco.org/content/115525-132; cited 24 May 2015]
76. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2014.* Toronto, ON: Canadian Cancer Society; 2014.
77. Dahabreh IJ, Terasawa T, Castaldi PJ, Trikalinos TA. Systematic review: anti-epidermal growth factor receptor treatment effect modification by *KRAS* mutations in advanced colorectal cancer. *Ann Intern Med* 2011;154:37–49.
78. Douillard JY, Siena S, Cassidy J, *et al.* Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–705.
79. Van Cutsem E, Köhne CH, Hitre E, *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–17.
80. Janakiraman M, Vakiani E, Zeng Z, *et al.* Genomic and biological characterization of exon 4 *KRAS* mutations in human cancer. *Cancer Res* 2010;70:5901–11.
81. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–42.
82. Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;23:3706–12.
83. Saltz LB, Clarke S, Diaz-Rubio E, *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013–19. [Errata in: *J Clin Oncol* 2008;26:3110 and *J Clin Oncol* 2009;27:653]
84. Van Cutsem E, Köhne CH, Láng I, *et al.* Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011;29:2011–19.

85. Bokemeyer C, Bondarenko I, Makhson A, *et al.* Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;27:663–71.
86. Venook AP, Niedzwiecki D, Lenz HJ, *et al.* CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with *KRAS* wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) [abstract LBA3]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/126013-144; cited 24 May 2015]
87. Heinemann V, von Weikersthal LF, Decker T, *et al.* FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–75.
88. Schwartzberg LS, Rivera F, Karthaus M, *et al.* PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type *KRAS* exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014;32:2240–7.
89. Cancer Care Ontario (CCO). About ColonCancerCheck [Web page]. Toronto, ON: CCO; 2015. [Available at: https://www.cancercare.on.ca/pcs/screening/coloscreening/cccworks; cited 15 January 2015]
90. Giardiello FM, Allen JI, Axilbund JE, *et al.* on behalf of the American Society for Gastrointestinal Endoscopy. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastrointest Endosc* 2014;80:197–220.
91. Levin B, Lieberman DA, McFarland B, *et al.* on behalf of the American Cancer Society Colorectal Cancer Advisory Group, the U.S. Multi-Society Task Force, and the American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130–60.
92. Canadian Partnership Against Cancer (CPAC). *Colorectal Screening in Canada: Program Performance Results Report, January 2009–December 2011.* Toronto, ON: CPAC; 2013.
93. Whitlock EP, Lin J, Liles E, *et al. Screening for Colorectal Cancer: An Updated Systematic Review.* Rockville, MD: Agency for Healthcare Research and Quality; 2008.
94. van Rossum LG, van Rijn AF, Laheij RJ, *et al.* Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;135:82–90.
95. Quintero E, Castells A, Bujanda L, *et al.* on behalf of the COLONPREV study investigators. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012;366:697–706.
96. Holme O, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev* 2013;9:CD009259.
97. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case–control study. *Ann Intern Med* 2011;154:22–30.
98. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1–8.
99. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139:1128–37.
100. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology* 2010;138:2044–58.
101. Lindor NM, Greene MH. *The Concise Handbook of Family Cancer Syndromes.* Mayo Familial Cancer Program. *J Natl Cancer Inst* 1998;90:1039–71.