



## Gastric and colorectal cancers

**REPORT FROM THE 18<sup>TH</sup> ANNUAL EASTERN CANADIAN COLORECTAL CANCER CONSENSUS CONFERENCE (EC5), ST. JOHN'S, NEWFOUNDLAND, SEPTEMBER 28 TO 30, 2017**

Elena Tsvetkova, MD, FRCPC, Grand River Regional Cancer Centre, Kitchener, Ontario

### ABOUT THE MEETING

The EC5 meeting was attended by experts in medical, radiation and surgical oncology, as well as pathologists from the major cancer centres across Eastern Canada. The meeting produced several consensus statements based on best available evidence. Topics discussed included gastric and colorectal cancers, and the role of genetic screening in patients with these malignancies.

In this review, we present a summary of the consensus statements developed on these topics. A full report will be published in *Current Oncology*.

### GASTRIC CANCER

Based on 2012–2014 data, approximately 0.8% of the North American population will be diagnosed with gastric cancer in their lifetime.<sup>1</sup> The hereditary form of diffuse-type gastric cancer (DGC) is often related to multiple mutations in the E-cadherin (CDH1) gene that are inherited in an autosomal dominant pattern.

#### Genetic consultation and testing

Consensus was reached on referral for genetic consultation. The population considered to benefit most from being tested for hereditary gastric cancer includes people who have:

- one case of DGC in the family diagnosed before the age of 40.
- two gastric cancers in the family, regardless of age, with at least one confirmed DGC.
- a personal history of lobular breast cancer (LBC) or family history of two or more cases of LBC, with one being diagnosed before the age of 50.
- a personal history of bilateral LBC or family history of two or more cases of LBC diagnosed before the age of 50.
- *in situ* signet ring and/or pagetoid spread of signet ring cells on gastric biopsy.

Further consensus recommendations for genetic testing include:

- For intestinal-type gastric cancer, genetic testing is not recommended.
- Patients with a strong family history of gastric cancer who tested negative for pathogenic mutations initially may be re-referred to genetics every 3 to 5 years for further testing.

- Each jurisdiction should take local patterns of incidence into consideration.
- Consideration also should be given to the increased risk of gastric cancer with other hereditary cancer syndromes, including: Lynch syndrome, familial adenomatous polyposis (FAP), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and Peutz-Jeghers syndrome.

Regarding the management of patients who are found to harbour the CDH1 mutation, the following recommendations achieved consensus:

- Prophylactic total gastrectomy with Roux-en-Y reconstruction should be recommended in early adulthood. The timing of surgery should consider family history of age of onset, as well as childbearing plans.
- Surgery should be performed in a centre of excellence. The surgical gastrectomy specimen must be examined using specific hereditary DGC protocols.
- For those who opt not to undergo prophylactic gastrectomy, regular annual endoscopy with random biopsies is recommended. However, it is important to ensure that patients understand the limitations of screening. Chromoendoscopy is not recommended.

#### Metastatic gastric cancer

In the management of patients with metastatic gastric cancer, the primary focus should be on symptom relief and quality-of-life improvement, with early referral to the palliative care team. Palliative surgical/endoscopic procedures should also be considered in symptomatic patients. Consensus recommendations for systemic treatment include:

- Combination chemotherapy is superior to single-agent therapy for overall survival, if the patient is fit.

- Upfront human epidermal growth factor receptor 2 (HER2) testing is mandatory to select an appropriate first-line therapy in gastric and gastroesophageal junction (GEJ) adenocarcinomas and should be done in designated centres. However, delays in obtaining test results should not delay commencement of palliative chemotherapy.
- Established first-line combination chemotherapy regimens for HER2-negative gastric cancer include ECX (epirubicin, cisplatin, capecitabine), ECF (epirubicin, cisplatin, fluorouracil), EOX (epirubicin, oxaliplatin, capecitabine), EOF (epirubicin, oxaliplatin, fluorouracil), FOLFOX (leucovorin, fluorouracil, and oxaliplatin), XELOX (capecitabine, oxaliplatin), CF (cisplatin, fluorouracil), CX (cisplatin, capecitabine), FOLFIRI (leucovorin, fluorouracil, irinotecan), DCF (docetaxel, cisplatin and fluorouracil), and modified DCF.
- HER2-positive gastric adenocarcinomas should be treated with first-line trastuzumab in combination with chemotherapy, typically cisplatin and fluorouracil/capecitabine (HCF/HCX). Prior ejection fraction evaluation with echocardiography or multiple-gated acquisition (MUGA) scanning is required.
- Strong consideration should be given to toxicity profile, patient preference and convenience when selecting therapies.
- Clinical trials should always be considered.
- Second and further lines of chemotherapy have been associated with improvement in overall survival and quality of life compared with best supportive care.
- Ramucirumab is an active treatment in the second-line setting in combination with paclitaxel. However, patients with stents should not be treated with ramucirumab, given the risk of perforation.
- Other active agents in the second-line setting include taxanes and irinotecan.
- Radiation therapy should be considered for symptom relief.
- Elderly patients with gastric cancer should be considered for systemic chemotherapy if performance status permits.
- The role of immunotherapy with programmed cell death ligand 1 (PD-L1) targeting agents in advanced gastric cancer is evolving. Emerging evidence has led to the approval of pembrolizumab in the United States.

## COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer in males and the second most common cancer in females.<sup>2</sup> Over the last decade, the rate of younger adults diagnosed with CRC has been increasing. In the United States, CRC is associated with known hereditary CRC syndromes in about one-third of cases in adults aged 35 or younger.<sup>3</sup> Following discussion of these issues, experts achieved a number of consensus recommendations for genetic screening and management of CRC.

## When should genetic screening be undertaken for CRC?

Recognition of hereditary CRC is important to allow genetic screening for patients and families at risk for hereditary CRC, to facilitate appropriate screening, and to provide early diagnosis and treatment. Genetic screening for CRC requires a multidisciplinary team that includes a genetic counsellor and dedicated genetics program.

Genetic screening may be performed in a number of ways, depending on the clinical situation, and should be selected in conjunction with the genetics department. It may involve:

- testing for specific mutation(s);
- testing for founder mutation(s) common to a specific region;
- testing for mutation(s) involved in a specific hereditary CRC in patients with an associated clinical phenotype;
- use of a select or custom commercial hereditary cancer gene panel;
- universal testing of all CRC patients with additional confirmatory testing.

---

In the setting of advanced CRC where patients are fit for treatment, the following recommendations achieved consensus:

- Extended RAS and BRAF V600 testing should be performed on patients with metastatic CRC in a timely manner, preferably from the metastatic lesion and most recent tissue available; the report should be available within 10 days; core biopsy is preferable over fine-needle aspiration.
- Microsatellite instability (MSI) testing should be done on all patients with CRC, regardless of cancer stage, in patients younger than 70 years of age.
- In patients who have MSI, intensive followup with the genetics department is warranted.

## Radiation, systemic and immune therapy

In considering radiation therapy in the management of rectal cancer, consensus was reached on the following statements:

- A short course of preoperative radiation therapy (RT) may be preferred over a long course of preoperative RT, with concurrent chemotherapy for T2–3 and any N, where the predicted resection margin is clear; studies show similar local control and overall survival between short- and long-course RT in this context.
- For patients who require downstaging but are not fit for chemotherapy, short-course RT followed by delayed surgery is an option.
- All cases should be discussed in a multidisciplinary setting, including surgical and radiation oncology, with consideration for the need for tumour downsizing, potential toxicities, patient preference and convenience.
- Participation in clinical trials is encouraged.

The approach to systemic therapy in metastatic CRC has evolved over time.

- In patients with RAS wild-type left-sided CRC, standard chemotherapy (FOLFOX or FOLFIRI) in combination with epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab) is recommended in the first-line setting.
- In patients with RAS wild-type right-sided CRC, first-line EGFR monoclonal antibodies are not recommended. The combination of bevacizumab with standard chemotherapy remains the standard of care for this patient population.
- Extended RAS testing should be available in a timely manner to allow the appropriate selection of a biologic agent for first-line treatment decisions.

In second- and higher-line treatment, the following recommendations achieved consensus:


- At this time, there is no evidence to support selective use of EGFR monoclonal antibodies in the second-line setting based on primary tumour location.
- Patients who have not been treated with bevacizumab in the first-line setting should be offered bevacizumab in combination with standard chemotherapy in the second-line setting.
- In the third-line setting, all RAS wild-type CRC patients who have not been treated previously with EGFR monoclonal antibodies should be offered one.
- At this time, there is insufficient evidence for selective use of EGFR monoclonal antibodies based on primary tumour location, where tumour response is the primary goal of therapy.
- Primary tumour location (PTL) should be factored into the design of future clinical trials in the treatment of RAS wild-type metastatic CRC.
- Given the fact that PTL is a surrogate for more complex biologic mechanisms, there should be ongoing research to understand patient- and tumour-related factors that underlie the observed differential benefits of biologics based on PTL.

In patients with CRC peritoneal carcinomatosis, the following recommendations achieved consensus:

- Palliative chemotherapy and supportive care remain the cornerstone of peritoneal carcinomatosis management.
- The role of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is evolving for select patients in experienced centres, with improvement in survival seen for some, but significant toxicity and morbidity.

- Patients should be reviewed by a multidisciplinary team, including surgeons and medical oncologists with experience in treating patients with peritoneal carcinomatosis.
- Further clinical trial data specifically relating to the need for HIPEC, appropriate patient selection, and need for neoadjuvant chemotherapy in conjunction with CRS and HIPEC are needed.

With regard to immune therapy in advanced CRC:

- It is recommended that patients undergo immunohistochemistry (IHC) for deficient mismatch repair (dMMR) proteins (MLH1, MSH2, PMS2, MSH6)
- Patients expressing both MLH1 and PMS2 likely have sporadic dMMR, and should be assessed for BRAF mutation (present in 50% of cases).
- Molecular testing laboratories are encouraged to develop next-generation sequencing (NGS) panels that include DNA polymerase delta 1/epsilon, catalytic subunit (POLD1/POLE) mutations (1–2% of CRC), or develop capacity to screen for hypermutation status.
- Patients with MSI/dMMR (and possibly POLD1/POLE mutations) have a high probability of response to programmed cell death 1 (PD1) or PD-L1 inhibitors, and should participate in immunotherapy trials, or have access to these agents off-label, pending Health Canada approval. 

**References:**

1. National Cancer Institute. Surveillance, Epidemiology, and End Result Program. Retrieved from: <https://seer.cancer.gov/statfacts/html/stomach.html>
2. Torre LA, Bray F, Siegel RL, et al. Global Cancer Statistics, 2012. *CA Cancer J Clin*. 2015 Mar;65(2):87-108.
3. Mork ME, You YN, Ying J, et al. High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults with Colorectal Cancer. *J Clin Oncol*. 2015 Nov 1;33(31):3544-9.