

MARCH 2021

LIVING WITH CANCER



COLORECTAL CANCER RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from March 1st 2021 to March 31th, 2021 inclusive and are intended for informational purposes only

MARCH 2021 PREVIEW

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SYSTEMIC THERAPIES, SURGERY & SCREENING

The gut microbiome and early age onset CRC: what are the connections?

March 2021

In recent years, the incidence of colorectal cancer (CRC), particularly cancer affecting the distal colon and the rectum, has been on the rise among young adults below the age of 50. Evidence suggests that the gut microbiome may influence the cancer development pathways in CRC and may be a contributing factor to the rising incidence among younger adults.

What is the gut microbiome?

The gut microbiome, also referred to as the gut microbiota, is the totality of microorganisms, including bacteria, viruses, protozoa, and fungi, and their collective genetic material present in the gastrointestinal tract¹. The gut microbiome plays an important role in facilitating nutrient absorption in the human body, synthesis of beneficial enzymes and vitamins (including B vitamins and vitamin K), and the production of short-chain fatty acids (SCFAs). SCFAs are the main by-products (metabolites) produced by the microbiota of the large intestine through the fermentation of indigestible fibres and starches and are an essential energy source for the cells of the gastrointestinal mucosa. A growing body of evidence demonstrates that SCFAs have anti-inflammatory, antitumorigenic, and antimicrobial effects against bacterial pathogens, and have been shown to play an important role in the maintenance of a healthy gut equilibrium (homeostasis) and proper immune function. Reduced levels of SCFAs in the gut are associated with the increased incidence of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease².

¹ Gut microbiome

<https://www.sciencedirect.com/topics/medicine-and-dentistry/gut-microbiome>

² Short Chain Fatty Acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases

<https://www.frontiersin.org/articles/10.3389/fimmu.2019.00277/full>

The gut microbiome varies with age, geography, ethnicity, and diet. The increased presence of certain bacteria, such as *Fusobacterium nucleatum*, have been associated with the development of colorectal and other gastrointestinal cancers by inducing inflammation and suppressing host immunity³, and has been implicated in about one third of all colorectal cancers⁴. Individuals who consume inflammatory diets enriched in refined foods and red meats and low in plant-based foods have a higher risk of *Fusobacterium*-associated CRC. These bacteria have been found to be more frequently present in cancers of the right side of the colon, with patients with *Fusobacterium*-positive CRC tumours often having worse prognoses and disease outcomes⁵.

Gut-immune connection and CRC development

The intestinal microbiome of a healthy person is a balanced community of microorganisms that maintain intestinal health and participate in the “training” of the immune system in effectively distinguishing between host and invader cells in the colon. The microbiome plays a critical role in developing major components of the host’s immune system, exerting an important influence on intestinal inflammatory responses⁶. It is understood that certain elements of the immune system that mediate chronic inflammation are associated with the development of CRC through various pathways such as increased DNA damage in the cells of the colon⁷.

In an ongoing comparison study that examined microbiome differences in younger vs. older-onset CRC, the researchers compared the microbiome found within tumours of CRC patients diagnosed before age 45 and after age 65. Both primary and metastatic tumours were included in the analysis. Findings demonstrated that *F. nucleatum* was present in a greater number of tumours in patients with CRC diagnosed before age 45⁸. The study is still recruiting patients with the goal of gathering larger sample sizes so that a clearer picture of the differences in the microbiome between older and younger patients can be obtained, and more conclusive evidence can be

³ *Fusobacterium nucleatum* contributes to the carcinogenesis of colorectal cancer by inducing inflammation and suppressing host immunity
<https://www.sciencedirect.com/science/article/pii/S1936523319300233>

⁴ Could the bacteria in our gut help treat cancer?
<https://scienceblog.cancerresearchuk.org/2019/03/21/could-the-bacteria-in-our-gut-help-treat-cancer/>

⁵ Could the bacteria in our gut help treat cancer?
<https://scienceblog.cancerresearchuk.org/2019/03/21/could-the-bacteria-in-our-gut-help-treat-cancer/>

⁶ Interaction between microbiota and immunity in health and disease
<https://www.nature.com/articles/s41422-020-0332-7#:~:text=The%20microbiome%20plays%20critical%20roles,features%20of%20host%2Dmicrobe%20sym%20biosis.>

⁷ The gut microbiome and potential implications for early-onset colorectal cancer
<https://www.futuremedicine.com/doi/full/10.2217/crc-2020-0007>

⁸ A comparison study of the intratumoural microbiome in younger vs older-onset colorectal cancer
https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.241

gathered to understand whether increased levels of *F. nucleatum* can help explain the rising incidence of EAO CRC.

In conclusion, it is clear that the trend toward increasing incidence of EAO CRC cannot be explained by hereditary syndromes alone - other contributing factors such as the impact of the gut microbiome must be considered. The microbiome is involved in many disease processes, and the growing number of studies focused on the microbiome and CRC suggest that the microbiome may play a more important role in cancer development and treatment outcomes than previously imagined. The impact of the gut microbiome on CRC risk and development is an important field of research that will continue to gather speed in upcoming years, with numerous research projects including the international OPTIMISTIC project focused on better characterizing the role of the microbiome in CRC.

Take away message:

The gut microbiome is the totality of microorganisms, including bacteria, viruses, protozoa, and fungi, and their collective genetic material present in the gastrointestinal tract. It plays an important role in the maintenance of health in the human body, and consequently, when it is disturbed, such as through diet and excessive antibiotic use, plays an important role in the development of disease including cancer. A growing body of evidence is showing the complex interconnection between the gut microbiome, the immune system, and cancer development.

READ THE FULL ARTICLE

The role of maintenance strategies in metastatic colorectal cancer

March 2021

Results from a systematic review published in *JAMA Oncology* found that maintenance chemotherapy following initial treatment appeared to be more beneficial for patients with metastatic colorectal cancer (mCRC) than continuing a full induction chemotherapy regimen until disease progression.

Systematic review: a review of a clearly formulated question that uses systematic and reproducible methods to identify, select and critically analyze all relevant research, and to collect and analyse data from the studies that are included in the review

Maintenance chemotherapy: chemotherapy given in lower doses to assist in prolonging a remission (Chemocare)

Induction chemotherapy: chemotherapy given before the initiation of another treatment. May also be referred to as neoadjuvant chemotherapy.

These findings suggest that for some patients, switching to a lighter, less intensive maintenance regimen of chemotherapy or even taking a break in treatment is appropriate, with a return to a full

chemotherapy regimen if the disease progresses. Given that the goal of therapy in mCRC is to prolong life while preserving or improving quality of life, it is important to make use of treatments that achieve the maximum benefit with the fewest side effects. Given that chemotherapy regimens come with varying levels of toxicity, gaining a better understanding of how to optimize treatment intensity and duration is of utmost importance.

Patients with advanced mCRC typically will receive chemotherapy in combination with a targeted therapy drug. The duration of first-line induction chemotherapy after achieving the maximum disease response has remained a subject of controversy due to the toxicities that can occur after prolonged treatment.

Results from the systematic review of the relevant randomized clinical trials found that there was no additional survival benefit of continuing full induction chemotherapy until progression compared with observation (no treatment). When compared to observation, patients who received maintenance chemotherapy experienced a progression-free survival benefit, but no overall survival benefit. All maintenance strategies, including 5-FU alone, and 5-FU in combination with bevacizumab, showed significant improvement in PFS compared to observation alone.

The researchers highlight that many chemotherapies are initially beneficial to patients in shrinking and controlling the cancer. After a few months of therapy, however, the maximum benefit is usually reached. At this point, the main focus might be directed towards how to best prolong that benefit while reducing toxicities and side effects. These study findings confirm that less-intensive chemotherapy regimens are appropriate and effective in prolonging progression-free survival outcomes, and that the use of more intensive chemotherapy regimens should be reserved for instances of disease progression.

Take away message:

Findings demonstrate that less-intensive maintenance chemotherapy may be an appropriate alternative for the treatment of patients with mCRC who have achieved maximum benefit from initial chemotherapy. Intensive chemotherapy can be reinstated if disease progression occurs, but lighter maintenance therapy can help to minimize toxicities and side effects while prolonging the anti-tumour benefits of initial chemotherapy.

[READ THE FULL ARTICLE](#)

Resistance to epidermal growth factor receptor inhibitors in metastatic colorectal cancer

March 2021

Cetuximab (Erbix) and panitumumab (Vectibix) are targeted therapies that are commonly used in the treatment of RAS wild type metastatic colorectal cancer (mCRC). These two drugs are antibodies that bind to the epidermal growth factor receptor (EGFR) on the surface of tumour cells. Once bound to the receptor, these drugs inhibit signalling that promotes further tumour cell proliferation and growth. While these therapies have contributed to improving patient outcomes, their use has been limited by the presence of pre-existing mechanisms of drug resistance or by the ability of cancer cells to develop resistance to therapy through time.

Research has been focused on the principal oncogenes – the genes that have the potential to cause cancer when mutated - in the EGFR pathway to better understand the ways that tumours can develop resistance to anti-EGFR therapies. New important results have been achieved, particularly among patients with mCRC who express the BRAFV600E mutation. BRAF inhibitors used alone demonstrate very limited results. “Vertical” blockade of the EGFR pathway, or the simultaneous blockade of several elements of the EGFR signalling pathway at once, has provided promising outcomes for this subset of mCRC patients who previously had very limited treatment options available, as seen in the BEACON CRC trial. This trial found that a combination therapy of an EGFR inhibitor with a BRAF inhibitor was able to effectively improve survival outcomes among patients with mCRC with the BRAFV600E mutation.

A novel strategy known as “rechallenge” aims to treat a colorectal tumour that has stopped responded or developed resistance to EGFR inhibitors to the same treatment after a specific interval of time in a later line of therapy. It is hypothesized that the mechanisms of resistance may become “undone” during this interval or break from therapy, allowing for better response rates to once again be achieved. Overall, results have been inconsistent due to differences in how patients were selected in the studies for rechallenge, as well as differences in the time intervals⁹. These inconsistencies highlight the need for further large-scale studies to determine the best treatment strategies.

While EGFR inhibitors are generally understood to have limited effectiveness in patients with mCRC that is RAS mutant, various strategies are underway to use different targeted therapy combinations to restore the tumour’s sensitivity to EGFR inhibitors. One such combination is the use of MEK inhibitors with cetuximab. Preclinical research in mice has shown that this combination resulted in a synergistic anti-tumour effect and increased mice survival, suggesting a potential rationale for testing this combination in the clinical setting.

The use of liquid biopsy analysis to get a better understanding of the dynamic molecular changes that occur throughout the evolution of CRC will provide a deeper understanding of the mechanisms that drive the evolution of acquired resistance to EGFR inhibitors¹⁰, enabling patients to be better selected for novel strategies such as the rechallenge strategy.

⁹ Mechanisms of Innate and Acquired Resistance to Anti-EGFR therapy: A review of current knowledge with a focus on rechallenge therapies
clincancerres.aacrjournals.org/content/25/23/6899

¹⁰ Longitudinal liquid biopsy and mathematical modeling of clonal evolution forecast time to treatment failure in the PROSPECT-C phase II colorectal cancer clinical trials

Take away message:

EGFR inhibitors such as cetuximab and panitumumab are commonly used drugs in the treatment of metastatic colorectal cancer. It is not uncommon, however, for tumours to develop resistance to these therapies, underlining the importance of gaining a better understanding of the various mechanisms of resistance.

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Swallowable capsule-camera instead of endoscopy for use at home

March 2021

The National Health Service (NHS) based in England will be conducting a study to examine the effectiveness of a miniature camera the size of a capsule that can be swallowed, and then transmits images of the gastrointestinal tract like an endoscopy or colonoscopy. The PillCam™ can be used by patients at home instead of having to visit a clinic or hospital for their screening test.

The tiny cameras pass through the body taking two images per second to examine for signs of cancer or other conditions such as Crohn's disease or ulcerative colitis. The trial will initially involve 11,000 patients from 40 regions across England. Participants will be sent the colon capsule to use at home. The capsule takes about 5-8 hours to pass through the entire digestive system.

The colon capsule comes at a time when many people are very cautious about going to a hospital, or their screening tests have been delayed or cancelled due to the pandemic. The colon capsule screening is a response to the surge of patients that sought colorectal screening after the dramatic slowdown in cancer services in 2020. In December 2020, 200,000 people came forward for screening in England, an increase of 13,000 compared to the same month in the previous year. The colon capsule is a promising new technology that could help to improve the early diagnosis of colorectal cancer and has the potential to improve outcomes for people who may be experiencing colorectal cancer symptoms and must urgently undergo further tests.

Take away message:

A novel technology known as a colon capsule uses a tiny, swallowable camera to image the gastrointestinal tract of patients. It will be evaluated in a study involving 11,000 patients across England to better understand the advantages and limitations associated with new technique. Its development came in response to the dramatic decrease in colorectal cancer screenings that occurred in 2020 due to the pandemic, and provides a potential alternative to in-person visits to the clinic or hospital.

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FDA will reassess 6 immunotherapy accelerated approvals

March 2021

The US Food and Drug Administration (FDA) introduced its Accelerated Approval Program in 1992 to allow for earlier approval of safe and effective drugs that:

- treat serious conditions in patients for whom few viable treatment options exist,
- show the potential for significant improvement over existing treatment options¹¹

This program allows approval to be based on the evaluation of a **surrogate endpoint**, which is a marker for a longer-term clinical outcome. Long-term clinical outcomes such as overall survival require years of ongoing monitoring and evaluation. Surrogate endpoints suggest that the long-term goal will be met, and therefore are used in accelerated approval processes to get the drug to the patients sooner. For example, a drug used to treat colorectal cancer is intended to increase the patient's life span. To definitively reach this end point, the clinical trial would require many years of monitoring and evaluating the patients who received the drug. A surrogate endpoint may be tumour shrinkage, because early evidence showed that the drug shrinks tumours and tumour shrinkage is an indicator of an improved cancer outcome.

Under the Accelerated Approval Program, drug companies still need to conduct studies to confirm the clinical benefit of the drug under review. These studies, known as phase 4 confirmatory trials or postmarketing surveillance trials, involve monitoring the safety and efficacy of the drug once it has been approved to be on the market. Findings from these trials determine whether the drug will receive traditional approval or is removed from the market.

Recently, six indications for immunotherapy drugs granted under the Accelerated Approval Program later failed to demonstrate clinical benefit of the drugs in confirmatory clinical trials. The FDA's Oncologic Drugs Advisory Committee (ODAC) will be holding a special three-day public hearing in April to allow for oncology experts and patients with cancer to share their input and perspective about the drugs, which include immunotherapy agents for certain types of breast cancer, bladder cancer, gastric cancers, and liver cancer. Based on the meeting, the ODAC will decide whether the drug approvals should be withdrawn and whether additional trials should be conducted¹². The immunotherapy drugs being reassessed include:

- Atezolizumab (Tecentriq, anti-PD-L1 antibody), for the treatment of specific subgroups of patients of metastatic breast and bladder cancer;

¹¹ Accelerated Approval Program

<https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-prog>

¹² FDA in brief: FDA Oncologic Drugs Advisory Committee to review status of six indications granted accelerated approval. FDA. March 11, 2021. Accessed March 21, 2021. <https://bit.ly/3cgG1bm>

- Pembrolizumab (Keytruda, anti-PD-L1 antibody), for the treatment of subgroups of patients with bladder cancer, gastric cancer, and liver cancer;
- Nivolumab (Opdivo, anti-PD-L1 antibody), for the treatment of a subgroup of patients with liver cancer.

The reassessment of these accelerated approvals is part of an industry-wide evaluation of accelerated approvals in oncology. This evaluation has led to the recent withdrawal of four other immunotherapy indications which were voluntarily withdrawn in consultation with the FDA, including nivolumab and pembrolizumab for the treatment of subsets of patients with metastatic small cell lung cancer. Since the creation of the Accelerated Approval Program, only 6% of accelerated approvals including these four recent withdrawals have been revoked. Indeed, the Accelerated Approval Program has been “an incredibly important mechanism to promote development of and access to therapies for serious or life-threatening illnesses”, according to a report by Friends of Cancer Research, an organization which drives collaboration among partners in research, policy and regulation to speed life-saving treatment to patients. Based on their 2020 report, cancer therapies approved through this pathway reached patients an average of 3.4 years sooner than if their approval status was dependant on a primary clinical endpoint such as overall survival for approval¹³.

Take away message:

Regulatory agencies such as the US Food and Drug Administration and Health Canada have accelerated approval programs and conditional approvals that enable drugs that treat life-threatening illnesses among patients with unmet medical needs to be approved for use sooner than through traditional approval pathways. In a small percentage of accelerated approvals, however, the drugs are withdrawn and undergo reassessment because they fail to show clinical benefit in phase 4 population-based clinical trials aimed at confirming the drug’s safety and effectiveness once it has been approved for market use.

[READ THE FULL ARTICLE](#)

¹³ Optimizing the use of accelerated approval. Friends of Cancer Research; 2020. Accessed March 11, 2021. <https://bit.ly/38vV28l>