

DECEMBER 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 December 1st 2021 to December 30th, 2021 inclusive and are intended for informational purposes only

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Association of TP53 mutations with outcomes in left-sided vs right-sided metastatic CRC

December 2021

TP53 is a tumour suppressor gene which provides the blueprint for a protein called tumour protein 53 or p53. This protein is a tumour suppressor, which regulates cell division and prevents cells from growing or dividing too quickly or in an uncontrolled manner. *TP53* mutations have been reported in up to 60% of colorectal cancer cases¹. The presence of this mutation has not been consistently shown to be an important predictive biomarker for CRC, meaning that having it does not clearly indicate an increased or decreased likelihood of a specific clinical event, such as disease recurrence or progression.

A recent study published in the *Journal of Clinical Oncology* found that when the tumour suppressor gene *TP53* was mutated and lost its function (a **loss-of-function mutation**), overall survival outcomes were worse among patients with metastatic right-sided colorectal cancer (CRC) compared to left-sided CRC. When *TP53* was mutated and its functioning augmented (**gain-of-function mutation**), poorer survival was found only in left-sided CRC tumours. These findings help to elucidate the role of *TP53* mutations within the context of metastatic CRC.

The study

Next-generation sequencing data from 1,043 patients from the Kaiser Permanente Northern California dataset were analyzed. The associations between gain-of-function/loss-of-function mutations and overall survival were analyzed using statistical modeling adjusted for age, sex, ethnicity, performance status, comorbidities and whether the patient received chemotherapy.

Findings

Among all patients, adjusted overall survival was similar between patients with *TP53* mutations compared to the unmutated wild-type gene. Overall survival was worse in right-sided vs left-sided CRC with *TP53* mutations. Overall survival was worse with gain-of-function mutations in left-sided CRC compared to right-sided disease, and for loss-of-function mutations, overall survival was worse in right-sided CRC. This study demonstrated how stratifying patients based on both *TP53* status and sidedness of their disease can provide new insight into their disease outcomes.

Take away message:

Findings from a recent study demonstrate the connection between mutations in the *TP53* gene, sidedness of colorectal tumours (left vs. right) and overall survival outcomes.

[READ THE ARTICLE](#)

¹ Lacopetta, Barry. Tp53 mutation in colorectal cancer. *Hum Mutat.* 2003 Mar;21(3):271-6. doi: 10.1002/humu.10175.

Update on the role of low-dose aspirin in colorectal cancer prevention

December 2021

In 2016, the United States Preventive Services Task Force (USPSTF) released a draft recommendation statement on the use of daily, low-dose aspirin to prevent cardiovascular disease (CVD) and colorectal cancer (CRC).

The USPSTF recommended initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50-59 who do not have an increased risk for bleeding, have a life expectancy of least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. For adults aged 60 to 69 years, the choice to take daily low-dose aspirin should be an individual one. For adults younger than 50 or older than 70 years, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CRC.

In late 2021, based on new analyses of the evidence from primary CVD prevention populations, longer term follow-up data from the Women's Health Study, and new trial evidence, the USPSTF concluded that the evidence is inadequate to support that low-dose aspirin use reduces CRC incidence or mortality.

It is important to note that the USPSTF is primarily challenged to provide broad, population-based recommendations. While there may be benefit to taking low-dose daily aspirin seen in narrowly defined populations that are treated in a specific way through clinical trials, it is difficult to take these findings and make them safely applicable to the population at large. For example, A recent study pooled data from two large cohort studies following a total of 94,540 patients and data on their aspirin use over some 35 years found that those who used aspirin before age 70 and continued into their 70s or later had a reduced risk of CRC but initiating aspirin at an older age was not linked with a lower risk of developing CRC. Such findings apply to a very specific cohort of individuals and while the USPSTF does tailor its recommendations on such factors as age, these categories may not be specific enough to optimally predict who will benefit from a cancer prevention agent such as aspirin.

Conclusions

While the USPSTF is not able to make a broad, population-based recommendation on the use of aspirin for CRC prevention, researchers underline the fact that this should not nullify the potential of a promising agent like aspirin which has a very long-standing body of literature about its safety profile and benefits. Instead of completely disregarding its potential as a cancer preventive, it will be important to instead refocus research efforts towards making sure that aspirin remains an option for the right patients.

Take away message:

The United States Preventive Services Task Force (USPSTF) recently updated its 2016 recommendations on low-dose aspirin use for the prevention of colorectal cancer, stating that evidence is inadequate to support its use in the primary prevention of the disease. These findings, however, may not be a reflection of aspirin's lack of benefit to individuals but rather the difficulty in transforming clinical trial data to a broad, population-based recommendation. Further research to refocus studies on aspirin and CRC to explore the benefit of aspirin in specific subsets of patients will be necessary.

READ THE ARTICLE

Overview of the CIRCULATE-Japan project: ctDNA testing to refine adjuvant therapy December 2021

The CIRCULATE-Japan project is comprised of three clinical trials which aim to evaluate the clinical benefits of using circulating tumour DNA (ctDNA) testing to refine precision adjuvant (post-surgical) therapy among patients with resectable colorectal cancer (CRC).

ctDNA is a non-invasive biomarker that can enable better tumour monitoring throughout a person's disease continuum. By monitoring ctDNA levels in the blood, clinicians can accurately detect minute quantities of residual tumour cells (**molecular residual disease**) and measure the therapeutic benefits of treatments. For example, a patient who receives chemotherapy can be monitoring using ctDNA to observe whether their tumours are responding to treatment, where ctDNA negative status is indicative of a response to treatment and low risk of cancer recurrence.

In the US, the Signatera™ (Natera, Inc) is a patient-specific, custom-built ctDNA monitoring test that tracks the presence of highly specific genetic material representative of the patient's unique tumours in the blood plasma. It is a highly sensitive test – it has shown over 95% sensitivity – indicating that it is very good at correctly identifying individuals with the disease. For example, one study that examined the effectiveness of Signatera™ found that among 122 patients with stage I to III CRC, ctDNA was detectable in 88.5% of patients prior to surgery. After treatment, long-term ctDNA analysis correctly identified 14 (87.5%) of 16 relapses².

The CIRCULATE-Japan project

The project is composed of one observational study and two randomized phase III trials:

² Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol.* 2019;**5**:1124-1131.

1. GALAXY study

This study is a large-scale nationwide registry designed to monitor ctDNA status in patients with stage II to IV CRC who are eligible for complete surgical resection of their tumours. The study involved taking blood samples from participants before surgery and at specified time intervals after surgery to perform ctDNA analysis using the Signatera™ tumour-informed assay. Patients with ctDNA negative status (i.e. low risk of cancer recurrence) at week 4 after surgery can be considered for enrollment into the VEGA trial; patients with ctDNA positive status at any time after standard adjuvant therapy can be considered for enrollment in the ALTAIR study.

2. VEGA trial

This trial aims to answer the question of whether to eliminate an immediate adjuvant chemotherapy for patients who are less likely to benefit from it. It is a randomized phase III trial designed to compare the effectiveness of adjuvant therapies in high-risk stage II or low-risk stage III CRC and evaluate how postoperative surgery compares to the standard combination chemotherapy regimen CAPOX (capecitabine plus oxaliplatin). If surgery alone proves to be equally as beneficial as chemotherapy, it will become the new standard of care in patients with ctDNA negative status 4 weeks after surgery, representing a significant treatment paradigm shift.

3. ALTAIR trial

This trial aims to evaluate the clinical significance of early intervention among patients with molecular residual disease (remaining tumour cells determined by ctDNA positive status) at an early stage by closely monitoring ctDNA status during the surveillance period after surgery. It is a randomized phase III study designed to evaluate the effectiveness of the chemotherapy drug trifluridine/tipiracil compared to placebo in patients with CRC who show ctDNA positive status with the Signatera assay at any time after curative resection for up to two months after their surgery. Trifluridine/tipiracil shows antitumor effects in tumours that are resistant to 5-FU based chemotherapy and has shown a survival benefit in chemotherapy-resistant mCRC. As such, it is hypothesized that this drug will have an antitumour effect on any existing molecular residual disease, including on tumours that are resistant to standard 5-FU based adjuvant therapy.

Conclusions

CIRCULATE-Japan project will not only create an important database for future reference containing ctDNA results, clinical outcomes and associated multiomics data (advanced biological data sets) in patients with CRC but will also evaluate the clinical importance of a ctDNA assay with high sensitivity and specificity as a guide for precision adjuvant therapy.

Take away message:

The CIRCULATE-Japan project is comprised of three clinical trials which aim to evaluate the clinical role of a ctDNA test with high sensitivity and specificity in guiding precision adjuvant therapy for patients with colorectal cancer.

READ THE FULL ARTICLE

Quality of life in a real-world study of patients with mCRC treated with Lonsurf

Trifluridine/tipiracil (commercial name: Lonsurf) is an oral medication that is approved by Health Canada for the treatment of adult patients with refractory (cancer that does not respond to treatment) metastatic colorectal cancer (mCRC) that have been previously treated with, or who are not candidates for, available therapies³. The approval was based on the results of the phase III RECURSE trial, which showed statistically significant survival benefits for patients with refractory mCRC who received Lonsurf compared to best supportive care. It was associated with few serious adverse events – the most common of which being neutropenia which occurred in 38% of patients compared to those who did not receive the drug⁴.

Both the US National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines include Lonsurf in the treatment algorithm for colon cancer as a preferred third-line choice for tumour reduction and disease control in patients who have RAS- and BRAF- mutated mCRC, and as a third-line choice in patients with RAS wild-type mCRC⁵, ⁶. Despite Lonsurf's inclusion in the international guidelines for colon cancer treatment and its approved for use in Canada, it is not reimbursed in most Canadian provinces and territories. Since August 2019, Lonsurf has been reimbursed only in Quebec under the Régie de l'assurance maladie du Québec⁷. In August 2019, the pan-Canadian Oncology Drug Review (pCODR) which makes

³ Health Canada. *Regulatory Decision Summary for Lonsurf [Web page]* Ottawa, ON: Health Canada; 2018. [Available at: <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00325>; cited 29 December 2021]

⁴ Randomized trial of TAS-102 for refractory metastatic colorectal cancer. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A, RECURSE Study Group. *N Engl J Med*. 2015 May 14; 372(20):1909-19.

⁵ National Comprehensive Cancer Network (NCCN) *NCCN Clinical Practice Guidelines in Oncology: Colon Cancer*. Ver. 1.2020. Fort Washington, PA: NCCN; 2019. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (free registration required); cited 29 December 2021] [Google Scholar] [Ref list]

⁶ ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Van Cutsem E, et al. *Ann Oncol*. 2016 Aug; 27(8):1386-422.

⁷ Régie de l'assurance maladie du Québec (RAMQ) *Demande d'autorisation de paiement – Médicaments d'exception [Web page]* Quebec City, QC: RAMQ; n.d.. [Available at: <http://www.ramq.gouv.qc.ca/fr/professionnels/pharmaciens/medicaments/medicaments-patient-exception/Pages/index-formulaires-mc.aspx>; cited 29 December 2021]

reimbursement recommendations for oncology pharmaceuticals across Canada with the exception of Quebec issued a negative recommendation, indicating that Lonsurf had only “potentially modest [progression-free survival] and [overall survival] benefit, moderate toxicities and an uncertain quality of life⁸, which means that patients who have mCRC outside of Quebec can only access this drug through private insurance or the Taiho Canada patient support program.

There is a high unmet need among patients with refractory mCRC for an effective and tolerable therapy option. A 2019 study found that more than 700 Canadians applied for the drug through the Taiho Canada patient support program over a one-year period⁹.

Quality of Life

Quality of life (QOL) is an important metric to individuals living with cancer and can influence their well-being and survival. Measures of QOL are now recognized as a key element to include in clinical trials and are typically captured through patient-reported outcomes. To date, there are few comparative studies that investigate the impact of Lonsurf on QOL compared to best supportive care for patients with mCRC. The PRECONNECT trial suggested that patients with mCRC treated with Lonsurf can maintain their QOL, but since there was no comparative arm, the trial was not able to show if patient QOL was **better** on Lonsurf compared to best supportive care.

The Study

A recent non-interventional study aimed to understand the difference in QOL for patients with refractory mCRC treated with Lonsurf or best supportive care in a real-world setting. Using three internationally validated QOL tools to capture patient QOL, the study also aimed to measure the differences in mCRC-related symptoms and pain between patients with mCRC who were treated with Lonsurf or with best supportive care.

Findings

Among the 105 patients included in the study, results showed that patients who received Lonsurf reported better overall QOL compared to those who received best supportive care. Patients who received Lonsurf reported less physical symptom distress, less psychological distress, lower activity level impairment, and better overall valuation of life.

The study’s focus on real-world outcomes captured the experience of patients who were being treated in a routine clinical setting, many of which may normally have been excluded from

⁸ Pan-Canadian Oncology Drug Review (PCODR) *pCODR Expert Review Committee (pERC) Final Recommendation [re. trifluridine and tipiracil (Lonsurf)]* Ottawa, ON: pCODR; 2019.

⁹ Real-world use of trifluridine/tipiracil for patients with metastatic colorectal cancer in Canada. *Samawi HH, Brezden-Masley C, Afzal AR, Cheung WY, Dolley A Curr Oncol. 2019 Oct; 26(5):319-329.*

standard, randomized clinical trials due to specific personal characteristics such as ECOG performance status or comorbidities.

There is evidence which shows that evaluating QOL and symptoms in a real-world context can help to improve patient satisfaction and symptom control, QOL, and is associated with better survival outcomes.

The study underlines the value of real-world QOL data in capturing the experience of patients with mCRC and are complementary to data collected from randomized clinical trials. Both datasets should be used to inform regulatory and health policy bodies about the urgent unmet clinical need among patients with refractory mCRC.

Take away message:

Real-world data from a recent study showed better quality of life outcomes for patients with metastatic colorectal cancer who received Lonsurf compared to best supportive care. The study highlights the importance of evaluating real-world data alongside data from randomized clinical trials to better understand the experience of patients in a real-world clinical setting.

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FDA clears new drug application for CAR-T cell therapy for the treatment of solid tumours

December 2021

This month, the Food and Drug Administration (FDA) cleared an investigational new drug application for a chimeric antigen receptor (CAR) T-cell therapy called P-MUC1C-ALL01, designed to treat adults with locally advanced or metastatic solid tumours. The investigational new drug application is specific to patients who are resistant to standard of care therapies or are ineligible to other existing treatment options.

CAR T-cell therapy is a type of immunotherapy approach that genetically engineers T cells, the “workhorses” of the body’s immune system, to produce receptors on their surface that allow them to recognize a specific protein, or antigen, on the surface of tumour cells. After the new T cells are made and their numbers expanded in the laboratory, they are infused into the patient who may have their total number of immune cells previously lowered through chemotherapy, enabling the novel T-cells a better chance to become activated, multiply, and fight the tumour cells. With the guidance from the engineered receptor, the novel T-cells recognize and kill cancer cells that express the targeted antigen.

In 2017, two CAR T-cell therapies were approved by the FDA – one for a type of childhood leukemia and the other for adults with advanced lymphoma. Thus far, the efficacy of CAR T-cell therapy in solid tumours has not been supported, and this therapy remains accessible through

clinical trials only. The recent FDA clearance will allow Poseida, the manufacturer of the P-MUC1C-ALL01 CAR T-cell therapy which targets tumours that express a cancer-specific form of the Mucin 1 protein on their surface, to begin enrolling patients in the clinical trial which will evaluate the therapy's safety, tolerability and efficacy among patients with advanced or metastatic solid tumours including breast, colorectal, lung, ovarian, pancreatic and renal cancers.

Take away message:

While CAR T-cell therapies have been approved in certain types of leukemia and lymphoma, their efficacy has not been supported among solid tumours. A CAR T-cell therapy manufacturer recently received approval from the FDA to begin enrollment for a clinical trial to evaluate the safety, tolerability and efficacy of a novel CAR T-cell therapy for the treatment of advanced solid tumours including colorectal.

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