AUGUST 2021

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

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Developing a better fecal immunochemical test (FIT) for colon cancer screening
August 2021

The fecal immunochemical test (FIT) is a widely used colorectal cancer (CRC) screening test that uses a specific antibody to detect hemoglobin in the stool, an indication of the presence of blood which can be an early sign of cancer. FIT can be sent to a person by mail and completed at home, and it does not require any type of bowel preparation to be done beforehand. In the instance that blood is detected in the stool, the individual will be referred by their doctor to have either:

- A colonoscopy, which uses a thin, flexible tube with a light and a camera at the end inserted into the rectum to examine the lining of the entire colon (large intestine)
- A flexible sigmoidoscopy, which uses a soft, flexible tube with a light and a camera at the end inserted into the rectum to examine the lining of the rectum and lower part of the colon (sigmoid colon).

The FIT is an appropriate test for the *initial* round of CRC screening because of its high diagnostic accuracy and higher participation rate compared to colonoscopy[1]. However, a major pitfall of FIT as a CRC screening method is that the detection rate and diagnostic capacity for advanced CRC adenomas and advanced serrated polyps is lower than that associated with colonoscopy.

Due to the need for a better non-invasive screening test that has a higher sensitivity (the ability of the test to correctly identify individuals with pre-cancer) for more advanced CRC adenomas without increasing overall false positives, a recent study conducted in the Netherlands aimed to evaluate the effectiveness of a multitarget FIT (mtFIT) which uses several different biomarkers in addition to hemoglobin used in the standard FIT.

The investigators found that mtFIT had significantly higher sensitivity than standard FIT for detecting advanced adenomas and an equivalent specificity (the ability of the test to correctly identify individuals *without* the disease) of 96.6%. For the detection of advanced adenomas, the mtFIT sensitivity increased by 35% compared to standard FIT (37.8% vs 28.1% respectively), while the sensitivity for detecting CRC remained the same[2].

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[1] Quintero E, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;**366**:697–706

[2] De Klaver, W., et al. Clinical Validation of a multitarget fecal immunochemical test for colorectal cancer screening. *Ann Intern Med.* [Epub ahead of print 20 July 2021]. doi:10.7326/M20-8270

The findings are important, as they show the benefit of relatively inexpensive improvements through the addition of specific biomarkers to the population-based FIT to increase its sensitivity.

Next steps

The research team will be preparing a large, prospective trial with 13,000 participants within the Dutch national CRC screening program in which mtFIT will be compared directly to the standard FIT, providing the final evidence on the sensitivity of the mtFIT compared to the standard FIT.

Take away message:

The fecal immunochemical test (FIT) is an important, population-based colorectal cancer (CRC) screening test that is highly effective at detecting early signs of cancer. A recent study evaluated the effectiveness of an improved FIT called the multi-target FIT (mtFIT) at detecting more advanced colorectal growths. Findings demonstrated that the ability of the mtFIT to detect these advanced lesions increased by 35% compared to standard FIT (37.8% vs 28.1% respectively), while the sensitivity for detecting CRC remained the same. Future studies will examine the effectiveness of mtFIT among a larger population size.

READ THE FULL ARTICLE

The importance of early screening for CRC in younger adults

August 2021

Earlier this year, the United States Preventative Services Task Force (USPSTF) updated their colorectal cancer (CRC) screening recommendations, stating that people of average CRC risk should start screening at 45 instead of 50 years old - a recommendation that echoes the American Cancer Society recommendation made in 2018. Until recently, if an individual was younger than 50, they would not get a colonoscopy unless they had CRC symptoms or had a family history of the disease. It remained unknown what types of colorectal abnormalities, such as type and stage of polyps, were present in individuals younger than 50.

Using a very large database, investigators analyzed data from about 3 million colonoscopies in the United States (with about 250,000 colonoscopies having been performed on individuals younger than 50). The study specifically looked at the data from patients between the age of 18-54 who received a screening or diagnostic colonoscopy and were not undergoing a colonoscopy to monitor any previously detected polyps, cancer, inflammatory bowel disease, or genetic conditions that predispose an individual to cancer. The findings were presented at the 2021 Digestive Disease Week and showed that:

- abnormal colorectal growths (**neoplasia**) were identified in 25.4% of screening procedures in patients aged 30 to 49 years[3], even though they did not have a documented family history of CRC
- 6.1% of these patients had **advanced** neoplasia, which is defined as either colorectal cancer or a benign tumour of the (**adenoma**) of at least 10mm in size
- About 0.53% of patients aged 40-44 were found to have CRC, and 0.58% of people between 45 and 49 had cancer, which turns out to be an incidence rate that is close to what is commonly seen in people older than 50 years

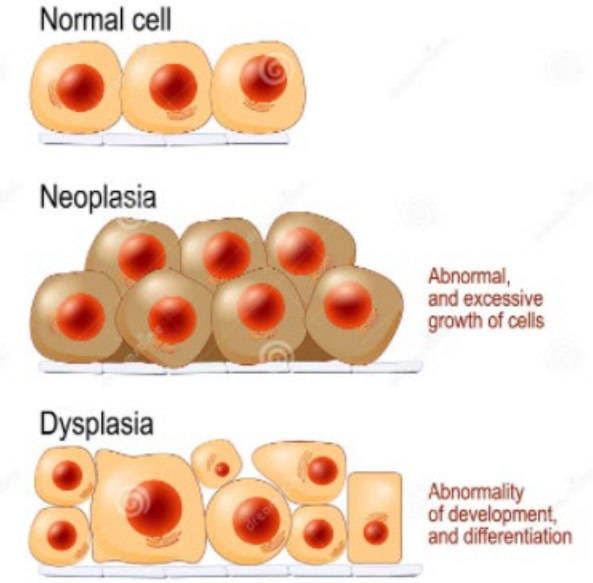

Image source: https://www.dreamstime.com/cancer-normal-cells-dysplasia-neoplasia-abnormality-development-differentiation-abnormal-excessive-growth-different-vector-image129589962

These findings are clinically significant as they are first to show the rates of important colorectal pathologies in people between the ages of 45-49 years, which help to further justify the lowering of the recommended starting colorectal screening age to 45. These numbers can then be used to perform various modeling analyses that examine cost-effectiveness and life-years gained from earlier screening.

Improving early messaging to young adults

The investigators highlight the central role of primary care physicians in conveying early messaging to individuals about CRC screening in their 30s and 40s. Since many young people below the age of 50 who get CRC do not have the typical risk factors that are seen in people over 50 such as obesity, sedentary lifestyle, smoking history, or family history, it is important to inform young people not to wait for symptoms to get checked. If a young person does present symptoms

[3]AMSURG and Mount Sinai Health System release new research on early-onset colorectal cancer. News release. Mount Sinai. May 24, 2021. Accessed August 10, 2021. https://bit.ly/3ustitb

such as rectal bleeding, a change in bowel movements, or sudden and unusual weight loss, they need to report to their doctor immediately and schedule a colonoscopy.

Take away message:
Findings from a recent study found that abnormal colorectal growths (**neoplasia**) were identified in 25.4% of screening procedures in patients aged 30 to 49 years. 6.1% of these patients had advanced neoplasia, which is defined as either colorectal cancer or a benign tumour of the (**adenoma**) of at least 10mm in size. About 0.58% of people between 45 and 49 had cancer, which turns out to be an incidence rate that is close to what is commonly seen in people older than 50 years.

READ THE ARTICLE

Clinical implications of the ongoing GALAXY trial

August 2021

Adjuvant (post-surgical) chemotherapy is useful in reducing the risk of disease recurrence and improving survival in patients who have undergone colorectal cancer (CRC) surgery. Analysis of circulating tumour DNA (ctDNA) levels pre- and post- surgery has potential applications as a predictive biomarker for selecting patients who are most likely to benefit from adjuvant chemotherapy.

The GALAXY trial is prospective, observational study (one that follows the participants over an extended period to observe long-term outcomes) that monitors the ctDNA levels before and after surgery in patients with stage II-IV CRC to observe how they correspond to disease outcomes. ctDNA contains the DNA (genetic material) from cancerous cells and tumours and can be detected in the bloodstream. Depending on the levels of ctDNA in the blood, information on the tumour status such as whether it has responded to treatment can be gathered.

Early findings from the study demonstrate that there is a very minimal difference in disease-free survival (DFS) among patients who have ctDNA present in the blood and those that do not *before* surgery. ctDNA levels, however, do provide important prognostic insight *after* surgery, where patients who are ctDNA negative post-surgery experiencing better disease outcomes. While evidence does support that ctDNA status can provide valuable insight into which patients are more likely to experience disease recurrence or worse outcomes, it is still not clear if ctDNA status can help to guide clinicians and patients in selecting the best treatment options.
Ideally, ctDNA can be used in the future to help stratify patients who may only need a less-intensive post-surgical treatment compared to those who would benefit from more aggressive treatment. As such, patients can receive the most tailored and effective treatment with minimal toxicity and intervention.

Take away message:

The ongoing GALAXY trial aims to monitor circulating tumour DNA (ctDNA) levels before and after surgery in patients with stage II to IV colorectal cancer to understand how they correspond to disease outcomes. Early findings show that pre-surgical ctDNA levels do not provide important insight into disease-free survival, while post-surgical ctDNA levels are more strongly associated with the patient's disease outcomes.

READ THE FULL ARTICLE

TRIBE2 trial: evaluating triplet vs. doublet chemotherapy for upfront treatment of metastatic colorectal cancer
August 2021

FOLFOXIRI is a triplet chemotherapy regimen consisting of folinic acid, 5-FU, oxaliplatin and irinotecan and is used in combination with the targeted therapy bevacizumab for the treatment of patients with metastatic colorectal cancer (mCRC).

Studies have shown that first-line triplet chemotherapy promotes better disease outcomes for patients compared to the doublet therapy FOLFIRI (fluorouracil, leucovorin, and irinotecan), but there is still uncertainty about the actual benefit of upfront exposure to three chemotherapy drugs compared to two, as well as the efficacy of the triplet chemotherapy after the cancer has progressed.
The TRIBE2 trial aimed to compare the efficacy of triplet versus doublet chemotherapy as upfront (initial) treatment of mCRC and after disease progression. The trial was a phase III study that randomly assigned patients with mCRC to received either:

- first-line doublet chemotherapy mFOLFOX6 plus bevacizumab, followed by FOLFIRI plus bevacizumab after disease progression (**control arm**)
- first line FOLFOXIRI plus bevacizumab, followed by the reintroduction of the same triplet therapy plus bevacizumab after disease progression (**experimental arm**)

Serious adverse events occurred in 25% of patients in the experimental arm compared to 17% in the control arm, with eight treatment-related deaths reported in the experimental arm and four in the control group.

Average progression-free survival (the amount of time the patient lives with the disease but it does not worsen) was 19.2 months in the experimental arm and 16.4 months in the control arm. Furthermore, a significant overall survival benefit was observed for patients receiving the triplet chemotherapy compared to the doublet. Serious adverse events after disease progression occurred in 15% of patients in the experimental arm and 12% in the control arm.
Overall, upfront FOLFOXIRI plus bevacizumab followed by the reintroduction of the same therapies after disease progression provided a statistically significant and clinically relevant progression-free and overall survival compared to first- and second-line doublet chemotherapy

plus bevacizumab in patients with mCRC. Furthermore, the median overall survival of 27.6 months was reached among patients receiving the triplet chemotherapy despite the high number of patients with poor prognostic biomarkers (RAS and BRAF mutations, right-sided tumours, synchronous metastasis (the diagnosis of distant metastasis together or within a three-month interval of the diagnosis of the primary colon cancer). These findings suggest that FOLFOXIRI plus bevacizumab may be a preferable treatment strategy for patients with mCRC.

Take away message:
Upfront first-line and second-line (after disease progression) triplet chemotherapy (FOLFOXIRI) plus the targeted therapy bevacizumab appears to be a better therapeutic strategy for patients with mCRC, promoting better disease-free and overall survival, compared to upfront doublet chemotherapy plus bevacizumab.

READ THE FULL ARTICLE

Impact of pain on employment and financial outcomes among cancer survivors
August 2021

Pain is one of the most reported symptoms among individuals with cancer. It may be caused by the cancer itself, cancer treatment (such as surgery), side effects of treatment (such as peripheral neuropathy), or a combination of different factors. Younger patients are more likely to have cancer pain and pain flares (a sudden, temporary increase in pain that may occur in patients who already have chronic pain from cancer or other conditions) compared to older patients[4]. Patients with advanced cancer experience more severe pain, and many cancer survivors have pain that continues after cancer treatment is over[5].

An American study aimed to better understand the role of pain levels on employment and financial outcomes among individuals with cancer. Using data from the 2016-2017 Medical Expenditure Panel Survey Experiences with Cancer Survivorship Supplement, about 1,200 adults diagnosed with cancer participated in the study. Statistical analyses examined the association between pain levels and self-reported employment and financial outcomes.

About 43% of adults with a cancer history reported no pain, 29% mild pain, 18% moderate pain, and 10% severe pain over the past 7 days. Those who reported any pain had significantly increased likelihood of adverse employment outcomes such as early retirement and feeling less productive. Individuals with any pain also had significantly greater chances of experiencing adverse financial outcomes such as borrowing money or going into debt, inability to cover medical costs, and worrying about paying medical bills compared to individuals who reported no pain. Greater pain

[4] Cancer Pain – National Cancer Institute
https://www.cancer.gov/about-cancer/treatment/side-effects/pain/pain-pdq

[5] Ibid

levels were associated with both employment and financial outcomes in a dose-response relationship, with worse pain resulting in worse employment and financial outcomes.

Since pain is among the most reported symptoms among individuals with cancer, these findings underline the importance of pain assessment strategies as part of the cancer continuum to employ strategies to support individuals living with cancer with their employment and financial objectives in order to improve patient-centred care.

Take away message:

Pain is one of the most reported symptoms among individuals living with cancer. A recent study aimed to evaluate the impact of pain levels on employment and financial outcomes. Greater pain levels were associated with worse employment and financial outcomes, underlining the importance of pain assessment strategies to better support individuals with cancer who experience greater levels of pain with their work and financial objectives.

READ THE FULL ARTICLE