MAY 2021

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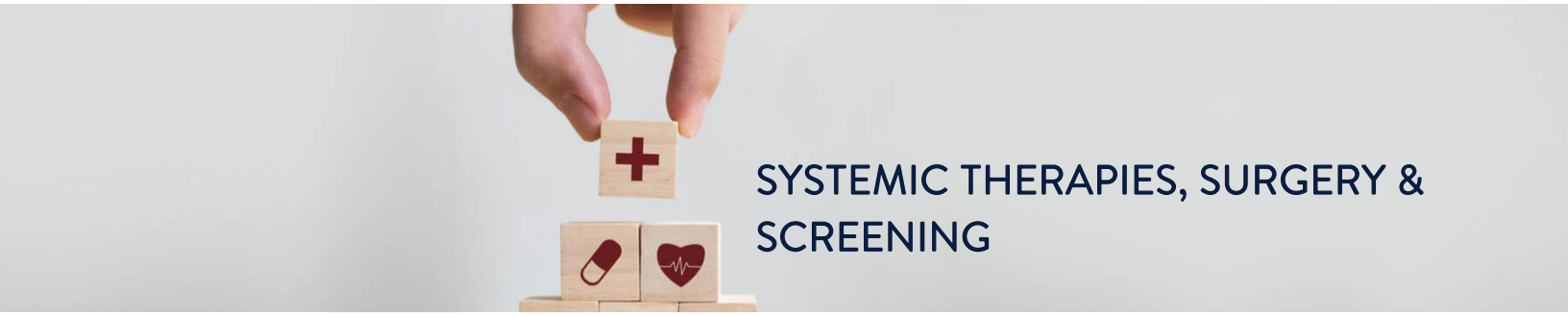
RESEARCH & PRACTICE UPDATES

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

MAY 2021 PREVIEW



SYSTEMIC THERAPIES, SURGERY & SCREENING

Is it time for universal genetic testing in colorectal cancer?
May 2021

Findings from a recent study show that multigene panel testing of patients with colorectal cancer (CRC) can detect inherited mutations that would not have been identified with guideline-based genetic testing.

The prospective study evaluated universal genetic testing, noting that 1 in 6 patients (16%) with CRC have an inherited genetic predisposition to the cancer. The study showed that more than half of patients with genetic mutations identified in the study would have been missed if they had undergone genetic testing based on current practice. 11% of the patients underwent a change in their treatment, such as the type of surgery or targeted therapy, based on their genetic findings. The study findings underline the limitations of exclusively relying on current clinical practice guidelines for genetic evaluation, which prioritize testing based on age at cancer diagnosis and family history of the disease.

The study
Researchers used a next-generation sequencing platform that included more than 80 genes in CRC patients. 361 patients with a median age of 57 years participated in the study. 15.5% of patients were identified to have germline mutations. The researchers found that younger age (under 50 years old) was associated with having a germline (inherited) mutation whereas gender, family cancer history, and stage of cancer were not. While current clinical guidelines rely on these characteristics to decide who should be referred for genetic testing, the study findings show that even older patients with CRC have a high rate of pathogenic germline mutations (12%) so by restricting genetic testing to only those under the age of 50 it is likely that clinicians “miss a substantial portion of patients who might benefit from this test.”

The study findings support wide use of genetic testing among all CRC patients, no matter what their age, gender, ethnicity, family cancer history or stage of cancer may be. More prospective

studies enrolling large numbers of patients from diverse backgrounds will be needed to best inform the development of best practice genetic testing guidelines.

Take-home message:
Current genetic testing guidelines for patients with colorectal cancer prioritize testing based on age at cancer diagnosis and family history of the disease. Findings from a study suggest that making genetic testing accessible to a wider range of CRC patients could help detect more inherited mutations, which could help to inform best treatment decisions.

READ THE FULL ARTICLE

USPSTF final recommendation on CRC screening: 45 is the new 50

May 2021

The final recommendation from the United States Preventive Services Task Force (USPSTF) builds on draft guidelines issued in October 2020 which state that screening for colorectal cancer (CRC) should now begin at age 45 and not 50 for average-risk individuals in the United States. The recommendation also mandates insurance coverage to ensure that all individuals have equal access to CRC screening regardless of their insurance status. Since most private health insurance plans as well as Medicare and Medicaid in most states follow USPSTF recommendations, these screening changes will be incorporated in their plans. The change might not be immediate, however, since insurance carriers generally update their coverage for the following plan year or exactly one year from the issue date of the recommendations.

These recommendations align with the American Cancer Society's 2018 recommendations to lower CRC screening to 45 years. The statistics on the alarming rise in the incidence of early age onset CRC have provided the substantial evidence for the change in recommendations, with CRC projected to be the leading cause of cancer death in patients aged 20-49 by 2040.

CRC risk factors

The USPSTF authors note that age is an important risk factor for CRC, with almost 94% of all new cases occurring in adults 45 years and older. Simulation models showed that beginning screening at 45 years of age was linked to an estimated 22-27 additional life years gained compared with starting at 50 years.

Screening recommendations

The updated USPSTF guidelines offer a variety of screening strategies, each associated with a different frequency of screening. These include:

- High sensitivity guaiac fecal occult blood test (FOBT) or fecal immunochemical test (FIT) every year
- Stool DNA-FIT every 1-3 years
- CT colonography every 5 years

- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years plus annual FIT
- Colonoscopy screening every 10 years

To best encourage screening and help patients select the best test, primary care clinicians play a critical role. They can help patients understand the pros and cons of various recommended options and ensure that patients seek out screening at the right time.

Current screening uptake
In the US, fewer than 70% of eligible patients currently undergo CRC screening. Lowering the recommended age to 45 is an important step forward in detecting CRC at an earlier stage and helping to direct patients to receive timely and appropriate treatments. With hope, many more lives can be saved by identifying the disease earlier when it most treatable. For young adults at a higher risk of developing CRC, such as those with a personal or family history of CRC or polyps or with Lynch syndrome, should talk to their doctor about their eligibility to start screening earlier than 45.

Take-home message:
The United States Preventative Services Task Force final recommendation on CRC screening suggest that among average-risk adults, screening should begin at 45 instead of 50. Informed by the statistics on the rising rates of early age onset CRC, these recommendations are an important step in increasing the availability of screening to younger individuals so that the disease can be detected at an earlier stage when it is most treatable.

READ THE FULL ARTICLE

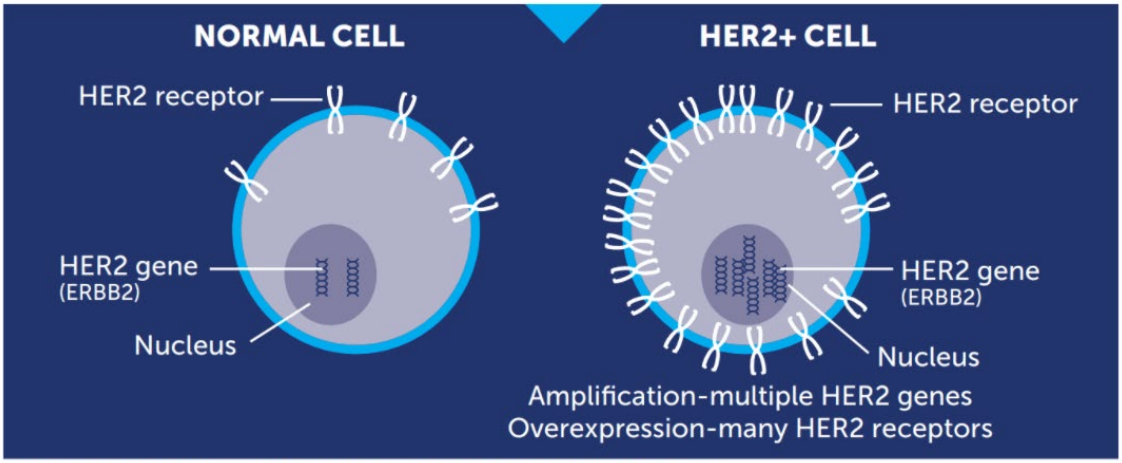
READ THE ARTICLE

Trastuzumab deruxtecan has promising activity in HER2+ advanced colorectal cancer
May 2021

The DESTINY-CRC01 trial is a phase II trial examining the safety and effectiveness of the antibody drug conjugate trastuzumab deruxtecan for the treatment of HER2-positive metastatic colorectal cancer (mCRC) that has been previously treated on standard therapies. This drug was originally developed for the treatment of HER2-positive breast cancer but has shown potential in the treatment of HER2-positive mCRC.

HER2, also known as ERBB2, is a gene that codes for a protein receptor found on the surface of almost all the cells in our body. It is part of the same family of protein receptors as the epidermal growth factor receptor (EGFR) which are responsible for promoting the growth, division, repair, and survival of cells. Some cancer cells have an overexpression or too many copies of the HER2

receptor on their cell surface, resulting in uncontrolled proliferation of the cells and eventually, a tumour.



Adopted from https://www.whathealth.com/breastcancer/her2receptor.html

Image source: Colorectal Cancer Alliance

About 2-4% of CRC tumours have an overexpression of the HER2 gene and receptor. It is more commonly found (6-8%) in CRC patients that are also wild type KRAS, and it is more commonly found in left-sided tumours than right-sided tumours[1]. HER2 amplification is not hereditary and instead happens as a random somatic change in the tumour cells. Currently, there are no approved therapies to target HER2-positive CRC.

The study

The DESTINY-CRC01 trial evaluated trastuzumab deruxtecan in 78 patients with HER2-expressing metastatic CRC that had progressed on two or more previous regimens, including other HER2-targeted therapies. Tumour regression and lasting responses were seen in most patients with HER2-positive tumours, leading to progression free survival and overall survival benefits. All patients reported a treatment-related adverse event, though most were low grade. Five patients (6%) experienced interstitial lung disease or pneumonitis, which accounted for the two drug-related deaths in the study. No responses with trastuzumab deruxtecan were observed in patients who had tumours with low to moderate expression of HER2, suggesting that the drug may only be effective when there is a minimum threshold amplification of the gene.

While trastuzumab deruxtecan shows promising and long-lasting results that highlight HER2 as an important biomarker in mCRC, the overall benefit of this treatment must be carefully considered alongside the risk of life-threatening toxicities such as pneumonitis.

Take home message:

[1] What is the HER2 biomarkers?
https://www.ccalliance.org/colorectal-cancer-information/biomarkers/biomarkers-her2

2-4% of patients with metastatic colorectal cancer overexpress the HER2 gene in cancer cells, resulting in their uncontrolled proliferation. Trastuzumab deruxtecan is a therapy that targets HER2 overexpression. In the DESTINY-CRC01 trial, tumour regression and lasting responses were seen in most patients with HER2-amplified tumours, though a small number of patients did experience life-threatening adverse events related to the drug.

READ THE FULL ARTICLE

Inflammosomes may play a role in obesity-related CRC

May 2021

Findings from a recent study show that protein complexes known as inflammasomes may be an important contributor to the development of obesity-related colon cancer. Inflammosomes are part of the innate immune system and help to regulate inflammation in the body, providing the first line of defense against pathogens. Dysregulation of inflammosomes within visceral adipose tissue (fat that surrounds the organs) and within the colon can trigger prolonged inflammation, which could favour the development of colon cancer. In the study, the intersection between chronic inflammation, obesity, and colon cancer development was examined and the results were presented during the virtual European Congress on Obesity on May 10-13, 2021.

The study

Tissue samples from 38 lean and 61 obese individuals were obtained and classified into those with or without colon cancer. Both obesity and colon cancer appear to increase the gene expression levels of several proteins involved in triggering inflammation (NLRP3, NLRP6, ASC, IL1B, and NOD2) in visceral adipose tissue (fat that surrounds the internal organs). The researchers also found evidence of a potential role for inflammasomes in changing the expression level of proteins that are involved in maintaining the integrity of the intestinal wall.

The findings shed light on the possible involvement of inflammosomes in obesity-associated colon cancer through the regulation of inflammation and intestinal-barrier integrity. In the future, strategies to restore the functions of inflammosome components could become a potential target to identify and treat patients with obesity at increased risk for developing colon cancer.

Take home message:

Protein complexes known as inflammosomes that make up part of our natural immunological defense may be involved in the development of obesity-related colorectal cancer through their regulation of inflammation and the integrity of the intestinal wall.

READ THE FULL ARTICLE

Study investigates nongenetic factors linked to the development of early-onset colorectal cancer

May 2021

A recent study published in *JNCI Cancer Spectrum* investigated whether the risk factors associated with late-onset colorectal cancer (CRC) were also relevant to early-onset disease, and whether these associations varied depending on the location of the primary tumour. The study is the first to examine non-genetic risk factors for early-onset CRC in a large patient population, paving the way for better targeted identification of individuals at higher risk of developing the disease.

Several non-genetic risk factors were found to be linked to increased incidence of early-onset CRC, including greater intake of red meat, lower educational attainment, and heavy alcohol use. Evaluating risk factors by anatomical site, the study revealed that a lower total fibre intake was linked more strongly to rectal cancer incidence compared to colon cancer. The researchers found that other CRC risk factors trended towards an association with early-onset disease, including a history of diabetes, as well as lower folate, dietary fibre, and calcium intake. With the alarming rise in the incidence of early-onset CRC in the past two decades, a better understanding of key risk factors is fundamental to mitigating the burden of this disease.

Take home message:

Findings from a recent study shed light on the non-genetic risk factors associated with the increased incidence of early-onset colorectal cancer. These include greater intake of red meat, lower educational attainment, heavy alcohol use, a history of diabetes, low folate, dietary fibre, and calcium intake. A better understanding of the key risk factors linked to early-onset disease is an essential first step to mitigating the burden of the disease.

READ THE FULL ARTICLE

IDEA trial establishes new standard of care for stage III colon cancer

May 2021

For patients with stage III colon cancer, the standard treatment has been 6 months of adjuvant chemotherapy after surgery. The IDEA (International Duration Evaluation of Adjuvant therapy) trial was designed to evaluate whether patients gained the same therapeutic benefit from 3 months of adjuvant chemotherapy vs. 6 months, with two standard chemotherapy regimens - FOLFOX (folinic acid, 5-FU, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) for high- and low-risk stage III disease. With the 5-year overall survival data, 3 months of adjuvant CAPOX can now be confidently recommended as the standard of care for stage III colon cancer patients.

The IDEA trial is the largest prospective trial to date that analyzes the effectiveness of adjuvant therapy in patients with colon cancer. The study pools data from six randomized phase III clinical trials that include over 13,000 patients followed over a period of 8 years.

Study methods

Patients with stage III colon cancer were randomly assigned to 3 or 6 months of either FOLFOX or CAPOX chemotherapy. Findings showed 5-year overall survival rates of 82.4% in patients who received 3 months of treatment compared to 82.8% in patients who received 6 months of treatment. While disease-free survival did not differ significantly between the 3- and 6-month CAPOX groups, it was significantly better with 6 months vs. 3 months of FOLFOX treatment. Expert analysis and clinicians have deemed the 0.4% difference In 5-year overall survival to be considered clinically nonsignificant, therefore supporting the use of 3 months of adjuvant CAPOX for most patients with stage III disease.

Clinical implications

Peripheral neuropathy is the most common long-term toxicity experienced from adjuvant chemotherapy for colorectal cancer and can be irreversible. The longer a patient is exposed to oxaliplatin-based chemotherapy, the more likely they are to develop this troubling side effect. In IDEA, the rate of grade 3 or greater neurotoxicity were 3% with 3 months of CAPOX compared to 9% with 6 months of CAPOX.

Shorter duration of CAPOX not only reduces peripheral neuropathy but also does not require an infusion pump or implantation of a vascular access device compared to FOLFOX therapy. 3 months on CAPOX also minimizes other common toxicities including diarrhea, neutropenia, nausea, mucositis, fatigue and hand-foot syndrome. A shorter treatment regimen that helps to minimize these side effects can have an important impact on patient quality of life and health care costs.

The slight benefit in disease-free survival seen with 6 months of FOLFOX therapy that was more pronounced among higher-risk patients must be considered alongside the increase in peripheral neuropathy rates – the rate of grade 3 or greater peripheral neuropathy is 3% with 3 months of FOLFOX compared to 16% with 6 months of the same treatment.

The findings from the IDEA study have led to updated guidelines for the treatment of this subset of patients, enabling patients to safely receive less chemotherapy and experience fewer distressing side effects without compromising their survival outcomes.

Take home message:

5-year overall survival outcomes from the IDEA study support the use of 3 months of adjuvant CAPOX chemotherapy compared to the previous standard of 6 months for most patients (i.e. those without high-risk disease) with stage III colon cancer. The shorter regimen promotes better quality of life by reducing distressing side effects such as peripheral neuropathy without compromising survival outcomes. The study findings have prompted a change in treatment

guidelines for this patient subset, while considering that high-risk stage III patients may still require 6 months of adjuvant chemotherapy if deemed necessary.

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