January 2022

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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 January 1st 2022 to January 30th, 2022 inclusive and are intended for informational purposes only

January 2022 PREVIEW

ASCO GI 2022: Key updates and important changes in CRC screening guidelines

January 2022

Colorectal cancer (CRC) screening means checking for the presence of the disease in someone who does not have any symptoms. To understand screening guidelines, it is important to first understand what is meant by average risk for CRC. There are several key questions that help to define a person's risk for developing the disease:

1. Have you ever had an adenomatous polyp (adenoma) or CRC?

Adenoma: *a benign tumour or growth that forms in a certain type of cell (glandular cell) that lines the inside of the intestine.*

2. Have any first-degree family members (parents, siblings) ever had an adenomatous polyp or CRC?
3. Do you have inflammatory bowel disease? e.g. Crohn's disease or ulcerative colitis
4. Do you have a hereditary syndrome that predisposes you to CRC? e.g. Lynch syndrome
5. Do you have a history of abdominal / pelvic radiation?

If the answer to all these questions is no, then a person is considered average risk. If the answer to any of these questions is yes, then a person may be at an increased risk of developing CRC and should talk to their doctor to develop an individualized screening plan.

CRC screening in average risk individuals

Currently, in Canada and the US, the CRC screening guidelines for average risk individuals are as follows:

- It is recommended to start CRC screening at 50 (Canada) or 45 (United States)

The starting screening age was lowered to 45 in the US following a 2018 update from the American Cancer Society, which took the rising rates of early age onset colorectal cancer into consideration. In Canada, there is currently no consensus on lowering the screening age to 45.

- Canadian recommendations: FIT every 2 years OR flexible sigmoidoscopy every 10 years (*Canadian Task Force on Preventative Health Care*)
- American recommendations: FIT every year OR flexible sigmoidoscopy every 5 years OR flexible sigmoidoscopy every 10 years + FIT every year OR colonoscopy every 10 years (*USPSTF*)

CRC screening in individuals at higher risk

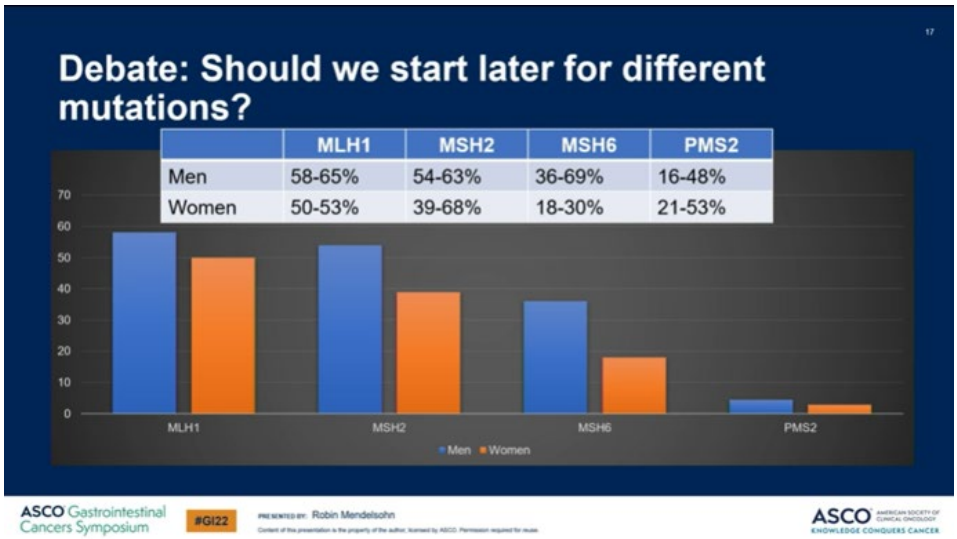
History	Recommendation
Lynch syndrome	Begin screening at 20-25, or 2-5 years younger than the youngest person in the family with a diagnosis, whichever earlier
First degree relative with CRC or advanced adenoma diagnosed <60 years old 2 first degree relatives with CRC or advanced adenoma	Begin screening at 40, or 10 years younger than age when youngest relative was diagnosed, whichever earlier
First degree relative with CRC or advanced adenoma diagnosed ≥ 60 years old	Begin screening at 40
Inflammatory bowel disease	Begin screening 8 years after diagnosis

Giardiello et al, GIE 2014; Rex et al. Am J Gastroenterol 2017; Rubin et al. Am J Gastroenterol 2019
http://www.survivorshipguidelines.org/

Lynch syndrome

Lynch syndrome is an inherited cancer syndrome that is associated with an increased chance of developing a range of different cancers including colorectal. It is the result of mutations or changes in genes that affect how DNA is repaired in the cell. When DNA is copied (an important precursor step to cell division and proliferation), mistakes can occur and are usually repaired by the cells' built-in repair mechanisms. In Lynch syndrome, the genes that regulate this repair mechanism are affected, which interferes with the cell's ability to repair DNA errors and prevent mutations from persisting in the cell. The inability to repair mistakes in the DNA is what eventually leads to the development of cancer.

There are 5 main genes that are associated with Lynch syndrome, and each one, when mutated, results in a different risk of developing colorectal cancer. As such, there has been debate about whether patients with different Lynch syndrome mutations should start CRC screening at different times.

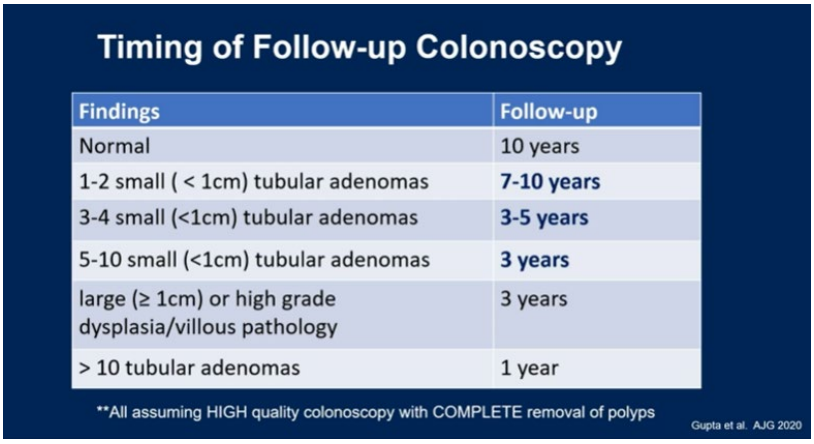


MLH1, MSH2, MSH6, and PMS2 are all Lynch syndrome-associated genes. The risk of developing CRC varies across these mutations, with the highest risk observed in patients who carry the MLH1 mutation.

For example, the National Comprehensive Cancer Network (NCCN) guidelines suggest that CRC screening begin at age 25-30 years for patients with Lynch syndrome who are *MSH6*- and *PMS2*-mutation carriers – slightly later than the overarching CRC screening guidelines for patients with Lynch syndrome.

Timing of follow-up colonoscopy

Once a person has completed an initial colonoscopy - for example, if they had a positive fecal immunochemical test (FIT) and went on to do a colonoscopy to investigate further – the timing of the following colonoscopy depends on the findings of the previous one:



ASCO GI 2022

The number of total adenomas that are found as well as the size and grade (how advanced they are with respect to becoming cancerous) are important factors to consider when planning the follow-up colonoscopy. Based on previous data, having no adenomas and finding 1-2 small adenomas

conferred a very similar risk for developing CRC, whereas the presence of just one high risk adenoma caused the resulting risk to increase more than 3-fold. As such, the findings are important determining factors to when the next colonoscopy should be scheduled.

When to stop CRC screening

The general recommendations for CRC screening in Canada and the US suggest continuing to age 74. At 75, the efficiency of screening declines, and the chance of screening-related risk factors (such as bowel perforation) increase. Therefore, from 75-85, it is recommended that the individual discuss the risks and benefits with their doctor to determine whether is it of value to continue screening.

Take away message:

CRC screening guidelines suggest that for average risk individuals, screening should start at 50 (Canada) and 45 (US). Screening begins earlier for individuals with a family history of the disease or polyps, inflammatory bowel disease, or genetic syndromes such as Lynch syndrome. There are suggestions to stratify patients with Lynch syndrome based on the mutation they have, though variations in these recommendations exist across the board. The timing of follow-up colonoscopies should be based on the previous findings, such as the total number and size/grade of polyps. Screening recommendations suggest stopping at 85, with discussion between the individual and physician for the period of 76-85 years to weigh the risks and benefits.

ASCO GI 2022: Phase I/II trial of encorafenib, cetuximab and nivolumab in patients with MSS BRAFV600E mCRC

January 2022

Based on the findings from the landmark BEACON CRC trial, the combination therapy of encorafenib + cetuximab was approved (FDA, Health Canada) for the treatment of patients with BRAFV600E-mutated metastatic colorectal cancer (mCRC). BRAFV600E mutations do not occur frequently in CRC (present in approximately 10% of CRCs), but they do confer a poor prognosis to patients. Since these patients do not respond well to standard therapies such as chemotherapy, the combination therapy fulfilled an unmet need for more effective treatment options.

A recent phase I/II trial (NCT04017650) aimed to explore the efficacy of adding immunotherapy to the above-mentioned combination therapy of encorafenib and cetuximab for patients with BRAFV600E mCRC. The patients who were included in the study specifically had microsatellite stable (MSS) tumours, an indication, on its own, that they are unlikely to respond to treatment with immunotherapy. However, in preclinical trials, the researchers found that treatment with a BRAF inhibitor (encorafenib) and an EGFR inhibitor (cetuximab) for patients with MSS BRAFV600E mCRC caused a switch from microsatellite stable status to microsatellite instability high (MSI-H) status, which is a predictor for positive response to immunotherapy. As such, the researchers

aimed to test this novel combination of immunotherapy plus targeted therapies in this patient subgroup.

Microsatellite instability high (MSI-H): *a biomarker that describes the condition of a tumour having a high likelihood of developing mutations, resulting from impaired DNA mismatch repair (MMR). A tumour that is MSI-H is characterized by a high number of mutations. This biomarker is present in about 5% of CRCs and is a predictor for positive response to immunotherapy.*

Microsatellite stable (MSS): *a biomarker that describes the condition of a tumour having a normally functioning DNA mismatch repair (MMR). The majority (95%) of CRCs are MSS. MSS tumours are characterized by low "detectability" by the body's immune system, which means that these tumours are not responsive to immunotherapy.*

The study

Patients with MSS BRAFV600E mCRC who had received one or two previous lines of therapy but no prior immunotherapy were enrolled in the study. The triplet combination of immunotherapy (nivolumab) plus encorafenib and cetuximab proved to be an effective and promising treatment in the context of the previously reported results from the BEACON study, resulting in a 50% overall response rate, with all patients achieving at least a partial response. The disease control rate was 96% among the 22 patients enrolled in the study. Furthermore, the combination therapy was well-tolerated by patients with no toxicities that caused patients to need to stop treatment. A phase II trial (SWOG 2107) to evaluate this combination of targeted therapies with or without nivolumab in a larger BRAFV600E MSS mCRC patient population across the US is currently underway.

Take away message:

Findings from a phase I/II clinical trial showed that the addition of immunotherapy (nivolumab) to the combination of targeted therapies encorafenib and cetuximab produced a high response rate and an acceptable safety and toxicity profile among patients with previously treated, microsatellite stable, BRAF V600E-mutated metastatic colorectal cancer.

READ THE ARTICLE

ASCO GI 2022: Trial evaluating immunotherapy in neoadjuvant setting for the treatment of locally advanced rectal cancer

January 2022

Total neoadjuvant therapy (TNT) is a standard approach for the treatment of locally advanced rectal cancer (stage II/III) that has been shown to produce better pathologic complete response (pCR), as well as improvements to disease-free survival (DFS), overall survival (OS), while reducing the risk of distant metastasis[1].

Neoadjuvant therapy: *therapy such as radiation or chemotherapy that is given before a main treatment, which is usually surgery.*

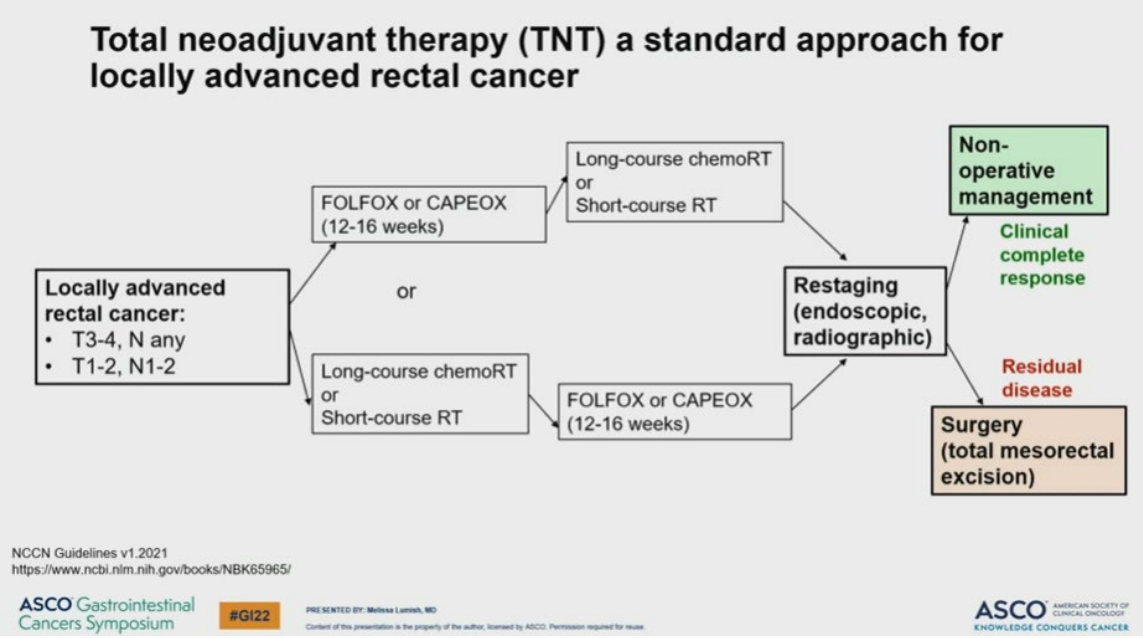
Pathologic complete response*: the lack of all signs of cancer in tissue samples removed after treatment with chemotherapy or radiation.*

Disease-free survival: *the amount of time a patient lives after treatment during which there are no signs and symptoms of the disease.*

Overall survival: *the time which begins at diagnosis or at the start of treatment up to the time of death.*

TNT aims to deliver an intensive pre-surgical, neoadjuvant treatment regimen to patients with rectal cancer through the combination of systemic chemotherapy with chemoradiation to improve pCR and survival rates.

1 https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1002/onco.13824#:~:text=The%20role%20of%20total%20neoadjuvant,survival%20compared%20with%20standard%20treatment.



Neoadjuvant chemotherapy in TNT usually consists of the combination regimens of FOLFOX (**fo**linic acid, **f**luorouracil and **ox**aliplatin) or CAPOX (**cap**ecitabine and **ox**aliplatin). This is either preceded or followed by chemoradiation consisting of either short-course or long-course radiation (choice between short-course and long-course radiation based on cancer centre protocol and patient's needs and preferences). This is followed by restaging of the cancer, and the option to proceed to surgery or not depending on the patient's response to neoadjuvant therapy.

Key considerations about rectal surgery

Rectal surgery is associated with higher rates of complications (e.g. sexual dysfunction, incontinence). As such, patients with rectal cancer who achieve a complete pathological response after neoadjuvant therapy may be considered for non-operative management, also known as "watch and wait" (WW). WW consists of very close surveillance and follow-up of patients who have achieved a complete response after TNT with the goal of avoiding surgery unless it is needed, such as in the case that the cancer comes back (cancer recurrence).

The study

MSI-H/dMMR tumours make up about 5-10% of all rectal cancer, and patients with this type of tumours have been shown to have an increased chance of progressing on neoadjuvant chemotherapy. While advanced rectal cancer that is microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) may be treated with immunotherapy, the use of immunotherapy in the ***neoadjuvant setting*** in patients with locally advanced disease has not been explored.

A recent phase II study (NCT04165772) aimed to evaluate the early use of immunotherapy as part of TNT for patients with locally advanced rectal cancer (stage II/III). Patients with stage II/III MSI-H dMMR rectal cancer received neoadjuvant immunotherapy (dostarlimab) with or without

chemoradiation as part of TNT for a total of 6 months. Patients first received immunotherapy, and those with any remaining disease after 6 months of treatment went on to receive standard chemoradiation. Following chemoradiation, any patients that did not reach a complete response were managed surgically.

Findings

Among the 13 patients enrolled in the study, none have required chemoradiation or surgery, and none have experienced any serious adverse events. As such, treating this subset of patients with neoadjuvant immunotherapy appears to be an effective and well-tolerated treatment that allows patients to avoid chemoradiation and surgery entirely, representing a novel strategy for treating MSI-H/dMMR rectal cancer. Long-term follow up and expansion of the study to evaluate this treatment approach in a larger patient population is ongoing.

Take away message:

The use of immunotherapy in the neoadjuvant setting appears to be a safe, effective and well-tolerated treatment for patients with MSI-H/dMMR locally advanced rectal cancer.

READ THE FULL ARTICLE

ASCO GI 2022: Short- vs. long-course chemoradiation in TNT

January 2022

In locally advanced rectal cancer (LARC) that has high-risk features (i.e. higher tumour stage, presence of tumour cells in the surrounding lymphatic and vascular systems), total neoadjuvant therapy (TNT) is the clear standard of care due to the increased disease-free survival (DFS) benefit associated with this treatment approach compared to neoadjuvant chemoradiation alone. However, in the key trials that provided the evidence to support the use of TNT in patients with LARC (RAPIDO and PRODIGE 23 trials), there was no indication as to whether short-course or long-course radiation was preferred.

Short-course radiation	Long-course radiation
25 grays over 5 days	50 grays over 25 days
Convenience for patient (and safety! COVID-19)	More inconvenient for patient (time off work, travel to hospital)
Lower healthcare costs	Higher healthcare costs
Similar disease control rates, safety and toxicity	

In several randomized controlled trials, it was shown that short-course and long-course radiation produced similar disease control rates, with comparable safety and toxicity. Overall, patients tend to prefer short-course radiation as it means less hospital time, and less time away from work and family. Compared to long-course radiation, short-course radiation shortens overall treatment time by about a month, which is a definite advantage especially during the COVID-19 pandemic. However, when a non-surgical watch-and-wait approach is desired by the patient, despite similar pathologic control rates there is a tendency among cancer centres to lean towards long-course chemoradiation as there is more data available on the use of long-course chemoradiation in a non-surgical approach.

Take away message:

Both short-course and long-course chemoradiation are reasonable and evidence-based radiation therapy options for TNT in patients with locally advanced rectal cancer (LARC). For most patients with LARC, short-course chemoradiation will give equal results to long-course chemoradiation and is preferred due to financial and logistical reasons. However, in a watch and wait approach, long-course radiation is preferred by many centres due to a more clinical data despite very comparable response rates to short-course chemoradiation.

ASCO GI 2022: Key considerations about oxaliplatin for the treatment of mCRC

January 2022

Oxaliplatin is an important intravenous chemotherapy drug that is used to treat advanced colorectal cancer (CRC). It is usually given in combination with other chemotherapy drugs, like fluorouracil and leucovorin (e.g. **FOLFOX** – **FO**linic acid + **F**luorouracil + **OX**aliplatin). Oxaliplatin is considered the most neurotoxic chemotherapy agent, affecting the normal activity of the nervous system. This drug is the cause of peripheral neuropathy, which can sometimes be irreversible. Symptoms include pain, a pins-and-needles sensation, numbness, and weakness. As such, oxaliplatin's efficacy in the treatment of mCRC is hampered by the dose-limiting neurotoxicity that may require dose reduction in order to prevent long-term neuropathy. The

following two studies examine the benefit of oxaliplatin in the treatment regimen of different subgroups of patients with CRC.

a) Understanding the benefit of oxaliplatin among older patients

According to findings from the phase III JCOG1018 RESPECT study, adding oxaliplatin to 5-FU-based chemotherapy plus bevacizumab did not benefit older patients with metastatic colorectal cancer (mCRC). The study results showed that adding oxaliplatin did not increase patients' progression-free survival (PFS) compared to 5-FU plus bevacizumab, and was associated with greater toxicity.

According to lead researcher Tetsuya Hamaguchi, MD, PhD, from Saitama Medical University International Medical Center in Japan, though 5-FU plus oxaliplatin with bevacizumab represents the standard, initial (first-line) therapy for patients with mCRC, since elderly patients are underrepresented in clinical trials, the benefit of this intensive first-line therapy in this subgroup of patients is not well understood.

Among the 251 patients with mCRC enrolled in the trial, 126 were randomly assigned to receive 5-FU plus bevacizumab with oxaliplatin and 125 were randomly assigned 5-FU plus bevacizumab alone. 5-FU-based chemotherapy was administered either as oral capecitabine or intravenous flourouracil plus leucovorin. The average age of participants in the oxaliplatin arm was 79 years, and 80 years in the no-oxaliplatin arm.

Patients who received oxaliplatin experienced more frequent adverse events compared to patients who did not receive oxaliplatin, including neutropenia (24% vs 15%), sensory neuropathy (57% vs 15%), fatigue (32% vs 21%), nausea (22% vs 10%) and diarrhea (16% vs 7%). The average PFS was 10 months in the oxaliplatin arm compared to 9.4 months in the no-oxaliplatin arm, while average overall survival (OS) was 19.7 months in the oxaliplatin arm and 21.3 months in the no-oxaliplatin arm. The overall response rate was 47.7% vs 29.5%, respectively.

Since oxaliplatin was associated with more adverse events and did not result in any significant improvements to PFS, the researchers concluded that 5-FU plus bevacizumab is the recommended initial treatment for elderly patients with mCRC.

READ THE FULL ARTICLE

b) Understanding the impact of removing oxaliplatin from adjuvant treatment for patients with stage III colon cancer

Among patients with high-risk stage III colon cancer, six months of oxaliplatin-based adjuvant chemotherapy (chemotherapy that follows surgery) is the standard treatment. While stopping

adjuvant treatment entirely could worsen patient outcomes, there is currently a lack of data on the impact of stopping oxaliplatin only.

The study

The research team led by Claire Gallois, MD, of Hôpital Européen Georges Pompidou in Paris aimed to understand two key points:

- the impact of stopping adjuvant treatment before the planned cycles have been completed;
- the impact of removing only oxaliplatin from treatment before the planned cycles have been completed.

Data from patients with stage III colon cancer who were enrolled in 11 relevant clinical trials within the ACCENT and IDEA databases were analyzed in this study. Both the Adjuvant Colon Cancer End Points (ACCENT) and the International Duration Evaluation of Adjuvant chemotherapy (IDEA) databases involve analyses of clinical data on the optimal use of adjuvant chemotherapy for patients with stage III disease. Patients were treated with a combination of leucovorin, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) prescribed for a duration of 6 months.

Findings

Once 75% of planned cycles had been completed, if oxaliplatin was removed it was not associated with worse disease-free survival (DFS) or overall survival (OS). However, if less than 50% of the planned oxaliplatin-containing chemotherapy cycles were completed and oxaliplatin was removed, patients experienced worse DFS.

In contrast, discontinuation of adjuvant treatment (stopping before 75% of planned chemotherapy cycles had been completed) was associated with a decrease in both DFS and OS.

Conclusion

Dr. Gallois concluded that among patients with high-risk stage III colon cancer prescribed a 6-month chemotherapy regimen, completing the planned number of treatment cycles appears to be important to DFS and OS outcomes. In patients who experience neurotoxicity due to treatment, the study findings do not support continuing oxaliplatin beyond 75% of the planned cycles. This underlines the central role of 5-FU-based chemotherapy in adjuvant chemotherapy for locally advanced stage III colon cancer.

Take away message:

Two studies evaluated the use of oxaliplatin in the treatment of different subgroups of patients with colorectal cancer. Since this chemotherapy drug is associated with potentially irreversible

nerve damage, understanding the minimum effective dose that can be safely administered to patients without negatively impacting survival outcomes is an important step towards improving the quality of life for patients undergoing treatment.

READ THE FULL ARTICLE

Can diet and lifestyle habits be used to predict cancer recurrence and death in patients with colon cancer?
January 2022

Current tools that are used to predict survival outcomes for patients with colon cancer rely mainly on clinical or pathologic characteristics, such as cancer stage at the time of diagnosis or tumour stage at the time of surgery. Increasing evidence suggests that diet and lifestyle habits are associated with patient outcomes and should be taken into consideration to create more accurate predictions.

A recent study aimed to develop tools (prediction models) to predict disease-free survival (DFS) and overall survival (OS) by incorporating patient-reported diet and lifestyle factors.

Methods and Results

Using two patient cohorts derived from clinical trials, the researchers developed predictive models based on the clinical, patholgoic, diet and lifestyle characteristics of patients with colon cancer to estimate their 5-year DFS and OS. Among the 1,024 patients included in the study, there were 394 disease recurrences and 311 deaths afer an average follow-up of 7.3 years. The researchers found that adding patient-reported diet and lifestyle factors to the clinical and pathologic characteristics meaningfully improved the prediction of patient outcomes.

Taking favourable diet and lifestyle factors into consideration, such as increased physical activity, improved 5-year DFS of all patients and improved 5-year DFS by 6.3% for patients with good-risk clinical and pathologic features, 21.4% for patients with average-risk clinical and pathologic features, and 42.6% for patients with poor-risk clinical and pathologic features. In other words, improvements to diet and lifestyle factors became increasingly important to improving 5-year DFS as clinical and pathologic features worsened.

Take away message

Diet and lifestyle factors can inform prediction models for recurrence and survival outcomes among patients with stage III colon cancer. These models could serve as important tools to predict patients' personalized survial outcomes. Through diet and lifestyle changes, patients can work together with their clinicians to meaningful impact their cancer outcomes.

READ THE FULL ARTICLE