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

JUNE 2021 PREVIEW

The PRODIGE 23 trial: neoadjuvant chemotherapy plus preoperative chemoradiation for patients with locally advanced rectal cancer
June 2021

For the management of locally advanced rectal cancer (LARC), main treatment goals are:

- to control local disease and promote survival
- target micrometastases
- improve quality of life.

Standard therapy for LARC includes chemoradiotherapy followed by surgery and adjuvant (post-operative) chemotherapy, but distant metastases remain common among patients. An alternative therapeutic approach known as total neoadjuvant therapy (TNT) involves giving chemoradiation plus neoadjuvant (pre-operative) chemotherapy prior to surgery with the goal of providing uninterrupted systemic therapy to minimize a patient's risk of developing micrometastases.

A systematic review and meta-analysis published in *JAMA Network Open* concluded that based on existing data, TNT appears to be a promising strategy for managing LARC, with better pathologic complete response rates (the absence of all signs of cancer) compared with standard therapy. TNT as an alternative treatment for LARC is now supported by the National Comprehensive Cancer Network[1].

The PRODIGE 23 trial is a phase III, multi-centre trial that aimed to assess whether an intensified preoperative chemotherapy regimen could reduce the risk of distant metastases. In the trial, patients with LARC were randomly assigned to receive either the experimental neoadjuvant chemotherapy group or the standard of care group. In the experimental arm, patients received:

- neoadjuvant chemotherapy with FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin), chemoradiotherapy (radiation therapy given in combination with oral capecitabine)
- followed by surgery (total mesorectal excision, or TME)
- followed by 3 months of adjuvant chemotherapy with FOLFOX6 (oxaliplatin and leucovorin, followed by intravenous 5-FU or oral capecitabine)

[1] Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774248

In the standard of care arm, patients received:

- chemoradiotherapy
- followed by TME
- followed by 6 months of adjuvant chemotherapy

From clinical trials and clinical practice, anywhere between 30-70% of patients who are candidates for post-operative chemotherapy either do not receive it, cannot tolerate it due to age, comorbidities, or toxicities. Therefore, in many cases, patients who might benefit from further systemic therapy to control the risk of metastases are not actually able to receive it. Pre-operative, neoadjuvant chemotherapy can often be given successfully, therefore resulting in improvements in disease-free survival.

Findings from PRODIGE 23 showed that by intensifying neoadjuvant chemotherapy with FOLFIRINOX, disease outcomes were significantly improved compared to the standard of care. The findings do support the use of TNT in improving disease-free survival as a more efficient and better tolerated approach than adjuvant chemotherapy, which may result in changes to clinical practice in the future. However, due to the toxicities that come with an intensive chemotherapy regimen such as FOLFIRINOX, there remains some doubt among clinicians whether the addition of irinotecan is beneficial and better than FOLFOX alone. Further investigation will be necessary to understand the how to best administer TNT, how much, to whom, and at what particular moment during a patient's course of treatment.

Take-home message:

Findings from the PRODIGE 23 trial support the use of total neoadjuvant therapy (TNT) for the management of locally advanced rectal cancer. TNT consists of a more intensive, pre-operative chemotherapy regimen that aims to deliver uninterrupted systemic treatment to better control the risk of metastases, which remain an important concern for patients with locally advanced disease.

READ THE FULL ARTICLE

The RAPIDO trial: short-course radiotherapy followed by chemotherapy before surgery for patients with locally advanced rectal cancer
June 2021

Among patients with locally advanced rectal cancer (LARC), distant metastasis remains a central concern even with postoperative adjuvant chemotherapy, likely due to many patients' inability to receive it because of comorbidities, toxicities, or age. The Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to minimize the risk of distant metastases, decrease disease-related treatment failure and maintain local disease control.

In the multicentre, phase III trial, participants with LARC were randomly assigned to receive the experimental treatment or the standard of care. The experimental arm consisted of short-course radiotherapy followed by CAPOX or FOLFOX4 chemotherapy, followed by surgery by total mesorectal excision (TME). Patients in the standard of care arm received long-course radiation in combination with oral capecitabine, followed by TME and if deemed appropriate by each hospital policy, adjuvant chemotherapy with either CAPOX or FOLFOX4.

The most common grade 3 or higher adverse events during preoperative therapy was diarrhea (18% vs 9%, experimental vs. standard of care arm) and neurological toxicity during adjuvant chemotherapy in the standard of care group (9%). Patients in the experimental arm experienced less chance of disease-related treatment failure as a result of a lower rate of distant metastases compared to the standard of care group. Patients in the experimental arm also achieved higher rates of pathologic complete response (the absence of all signs of cancer), which is a clinical indicator that allows patients to be considered for non-invasive, organ-preserving therapeutic approaches such as watch-and-wait. These findings are likely due to the increased efficacy of preoperative neoadjuvant chemotherapy compared to adjuvant chemotherapy, allowing the experimental treatment to be considered as a new standard of care.

Take-home message:

Findings from the RAPIDO trial showed the benefits of short-course radiation and preoperative chemotherapy compared to long-course radiation and post-operative chemotherapy for the treatment of patients with locally advanced rectal cancer, with the goal of controlling local disease and preventing distant metastases.

READ THE ARTICLE

Long-term follow-up supports watch and wait in rectal cancer
June 2021

The watch-and-wait strategy is a non-surgical therapeutic approach for managing locally advanced rectal cancer (LARC). In patients with LARC, the standard of care is chemotherapy and radiation (**chemoradiotherapy**) followed by surgery and post-operative adjuvant chemotherapy. Since rectal surgery is associated with significant morbidity and decreased quality of life, viable alternatives that maintain or improve quality of life without compromising patient survival outcomes are important and necessary.

The watch-and-wait strategy was originally proposed by Dr. Angelita Habr-Gama and her group in São Paulo, Brazil, who questioned the effectiveness of radical surgery in all patients diagnosed with LARC. Dr. Habr-Gama and her team have been researching the non-surgical management of LARC for almost 20 years in patients who achieve a pathologic complete response, or absence of all residual cancer cells, after initial treatment with chemotherapy and radiation. Among such

patients, findings from their studies have shown that overall survival rates are comparable to those from patients who undergo rectal surgery. Based on the available data, 10-25% of patients with LARC achieve a pathologic complete response after neoadjuvant treatment[2].

In a typical course of treatment with the watch-and-wait approach, there are three main components. First is radiation and chemotherapy given for about 6 weeks, then eight cycles of chemotherapy over four months[3]. This first part of treatment is known as total neoadjuvant therapy. Then the patient pauses for a few months, which is the second component of treatment. This allows the treatments time to shrink or destroy the tumour. If the tumour disappears completely (**pathologic complete response**), then the patient goes on to the third component, which is very close monitoring of the person with many different exams every year for 5 years. In the instance of cancer recurrence, the patient is referred for surgery.

Patients with rectal cancer who have a tumour in the lower half of the rectum are appropriate candidates for watch-and-wait. This is because this area is most difficult to perform successful surgery without compromising normal function.

Using follow-up results from the International Watch & Wait Database, the largest database of patients who underwent a watch-and-wait approach, the probability of remaining free of local regrowth for an additional 2 years increases with every additional year of continued pathologic complete response, with a 97% chance after 3 years, and 99% after 5 years. The probability of remaining free from distant metastases for a further 2 years in patients with a pathologic complete response without distant metastases for 1 year was 94%, 3 years was 98%, and for 5 years was 98%. Given that watch-and-wait demands very frequent follow-ups, these new findings suggest that the intensity of surveillance could potentially be reduced over time in patients who continue to present no residual cancer cells.

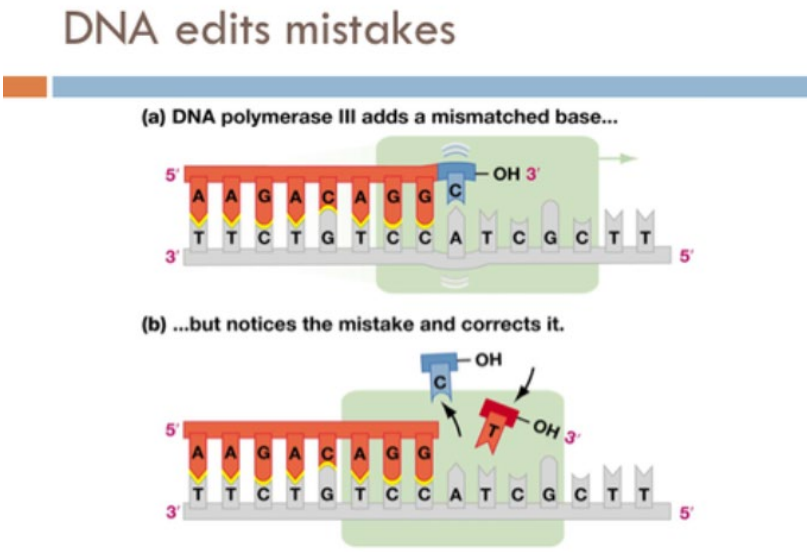
Take home message:
The watch-and-wait strategy is an alternative, non-surgical approach to managing locally advanced rectal cancer. It allows patients who have no evidence of cancer cells after initial chemotherapy and radiation to omit surgery and instead participate in very close surveillance, consisting of frequent follow-up and exams every year for 5 years.

READ THE FULL ARTICLE

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7422545/
[3] https://www.mskcc.org/news/how-watch-and-wait-approach-may-help-people-rectal-cancer-preserve-their-quality-life

A case-based approach to understanding complex genetic information in an evolving landscape: Lynch syndrome
June 2021

Lynch syndrome is an inherited cancer syndrome that increases a person's chance of developing different types of cancer including colorectal cancer. Also known as hereditary non-polyposis colorectal cancer, Lynch syndrome occurs when someone inherits specific mutations in genes that are involved in a process known as **DNA mismatch repair.** This process checks DNA after it has been copied and reproduced to make sure that no errors are present.



Lynch syndrome is defined by the presence of a mutation in any of the genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Lynch syndrome causes the following general lifetime cancer risk:

- 20-80% colorectal cancer
- 1-13% stomach cancer
- 1-4% liver/bile duct cancer
- 1-18% urinary tract cancer
- 1-6% small intestine cancer
- 1-6% pancreatic cancer
- 1-3% brain or central nervous system cancer

And in women:

In addition to the above risks:

- 15-60% endometrial cancer

- 1-38% ovarian cancer

(Cancer.net)

While most of colorectal cancer is **sporadic** and occurs without known contribution from inherited conditions, family cancer history or inflammatory bowel disease, about 3-5% of cases are attributed to Lynch syndrome. About 1 in 300 people in the general population will have Lynch syndrome.

Due to the increased risk of developing various types of cancer, it is recommended that people with Lynch syndrome participate in more rigorous cancer screening. General screening and risk-reduction guidelines include:

- Colonoscopy every 1-2 years, starting between the age of 20 and 25 or 5 years younger than the earliest age at diagnosis in the family – whichever is sooner
- Upper endoscopy every 3-5 years
- Consideration of a daily aspirin, which has been shown to be associated with a lower risk of colorectal caner and possibly other cancers in people with Lynch syndrome

Screening for women

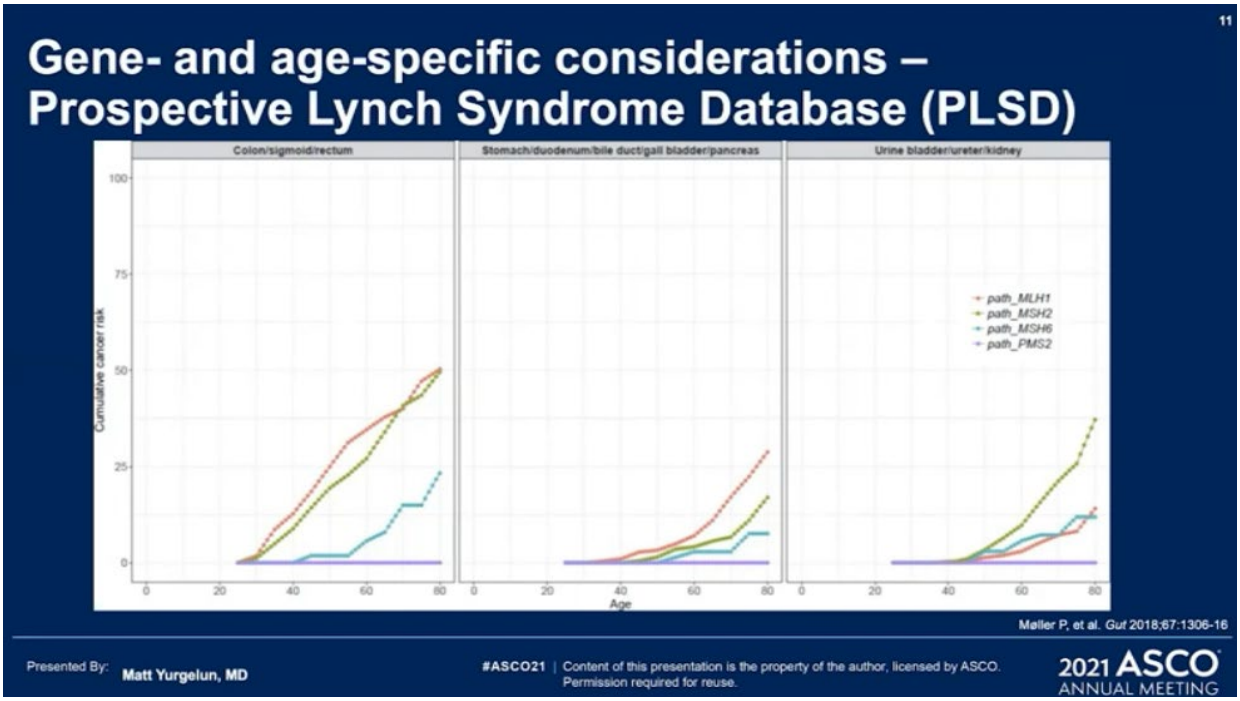
In addition to the above guidelines:

- Yearly pelvic examination, pelvic ultrasound, endometrial biopsy, from age 30-35. Women who do not plan to have any more children may want to consider surgical removal of the uterus and ovaries

Screening for other cancers that are linked to Lynch syndrome may occur based on a person's specific family history, but the effectiveness of such screening remains unclear. In the past, a "one size fits all" approach was applied to individuals with Lynch syndrome regardless of the patient-specific factors. Today, it is now clear that patient-specific factors such as sex and which gene mutation(s) (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM)* the patient has will influence the risk of developing each cancer type. A very intensive screening approach is now considered to be "overkill" for most people with Lynch syndrome, with the only interventions with good quality evidence to support their effectiveness in reducing cancer incidence and mortality being daily aspirin, hysterectomy (surgical removal of the uterus) and colonoscopy.

Current research efforts have been focused on understanding how to create more personalized risk assessment profiles for specific Lynch-associated cancers based on non-modifiable risk factors (sex, age, gene mutation, family cancer history) and modifiable risk factors (screening, medications such as aspirin, lifestyle factors such as diet and exercise, and environmental factors which are not well understood).

The European Prospective Lynch Syndrome Database arose from the need to report more reliable long-term results of people with Lynch syndrome and to increase knowledge about gene, sex, organ, and age-specific cancer risk. One of the primary findings from the Database showed that organ specific cancer risks and **penetrance** (the number of patients who have Lynch syndrome who develop a specific cancer) vary depending on which of the Lynch syndrome gene is present.



For example, patients with mutations in *MLH1 and MSH2* have a high risk of developing colorectal cancer (CRC) in the future. The risk of developing CRC was less for patients with a *MSH6* mutation, and even less for patients with a *PMS2* mutation.

When analyzed with respect to gender, the Database showed that *MLH1*-associated Lynch syndrome caused a 71% lifetime risk of any cancer in males, and 81% risk in females. Looking specifically at gastrointestinal cancers, *MLH1* mutations appeared to elevate lifetime risk of CRC more strongly in males (57%) than in females (48%). *MSH2*-associated Lynch syndrome has particularly high penetrance, with a lifetime risk of developing any cancer 75% in males and 84% in females. Another important finding from the Database demonstrated that participating in surveillance colonoscopies result in reduced cancer specific mortality but did not significantly impact cancer incidence.

These findings highlight the importance of a patient-specific approach to cancer screening for individuals with Lynch syndrome, addressing differences in gender and gene mutations as part of a more personalized approach to risk reduction.

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