DECEMBER 2020 PREVIEW

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New standard emerges for locally advanced rectal cancer
18 December 2020

Findings from phase III of the RAPIDO trial have shown that a new treatment approach for patients with high-risk, locally advanced rectal cancer reduces the rate of treatment failure and may help to better preserve organ functioning compared to the standard of care approach.

In locally advanced rectal cancer, the disease has spread to the surrounding connective tissue, known as the mesorectal fascia. The standard treatment for patients includes:

- Preoperative capecitabine chemotherapy given simultaneously with long-course radiation therapy;
- Followed by surgery by total mesorectal excision;
- With or without postoperative CAPOX or FOLFOX4 chemotherapy

In the RAPIDO trial, patients in the experimental arm received:

- Preoperative short-course radiotherapy;
- Followed by CAPOX or FOLFOX4 chemotherapy;
- Followed by surgery by total mesorectal excision.

Patients who received the novel treatment approach showed reduced disease-related treatment failure at 3 years compared to the standard treatment. The experimental treatment also doubled the rate of pathological complete response (the absence of residual cancer cells), which may permit more patients to seek out alternative, organ-preserving nonsurgical treatment options, such as the watch-and-wait approach. Overall survival at 3 years between the two treatment groups was similar.

According to the study researchers, “The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting.” A significant benefit of the experimental treatment is the reduction in the patient’s hospital stay – a benefit that is especially important in the era of COVID-19. They concluded that “the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer”.
Take away message:

A new treatment approach for patients with high-risk, locally advanced rectal cancer has shown to be superior in improving disease outcomes compared to the standard of care. The new protocol involves short-course radiotherapy followed by chemotherapy, followed by surgery by total mesorectal excision. Numerous additional benefits can be attributed to this novel treatment approach, including shorter hospital stay and an increase in the number of patients who become eligible for a watch-and-wait strategy, which promotes better organ preservation and resulting quality of life.

Targeting KRAS: Breakthrough therapies for a common mutation
14 December 2020

Kirsten rat sarcoma viral oncogene homolog, or KRAS, is one of the most commonly mutated oncogenes in cancer, and is mutated in about 20% of all cancers. An oncogene is any gene that has the potential to cause cancer.

KRAS belongs to the RAS protein superfamily and is involved in an array of signalling pathways in the cell, from proliferation to cell death.

Currently, there are no available therapies that directly target KRAS. While there have been many attempts, they have been largely unsuccessful because KRAS itself does not have the same
structural targets that other “druggable” proteins have. Targeting downstream proteins of KRAS, or proteins that KRAS activates later on in the signalling pathway, has also been unsuccessful because of two main reasons:

- KRAS turns on *multiple* important downstream pathways and inhibiting just one is often insufficient at controlling the cancer;
- inhibiting combinations of these downstream pathways often leads to unacceptable toxicities in the patient.

A breakthrough came in 2013 when a strategy was developed to directly target a specific variant of KRAS known as G12C. This specific KRAS mutation represents about 3-5% of colorectal cancers. Several inhibitors that target this mutation are in development and use highly specific immune-mediated inhibitors that selectively attack the mutated cancer cells and not wild-type KRAS proteins, therefore sparing healthy cells.

Another targeted approach to KRAS mutations is to target molecules that directly interact with KRAS. One target has been SOS1, with an inhibitor know as BI 1701963. This inhibitor is currently in clinical trials to evaluate its effectiveness at disrupting KRAS signalling and will be studied in combination with drugs such as adagrasib, which directly target the G12C KRAS mutation.
While it is a huge step forward in the field of oncology to observe clinical responses to KRAS inhibitors, overall, response rates remain low. An important reason for this is that feedback loops through the EGFR receptor are activated following KRAS G12C inhibition, leading to reactivation of the RAS signalling pathway.

Early but promising results are being seen with single agent inhibitors of KRAS G12C, and combination therapies which join receptor TRK inhibitors with immune checkpoint inhibitors are currently in development.

**Take home message:**

KRAS is the most commonly mutated gene in human cancers, yet remains a difficult target for cancer therapies. Several novel approaches are underway to inhibit specific mutations of KRAS, such as G12C, or specific proteins involved in KRAS signalling such as SOS1, with hope that this important oncogene can be addressed safely and effectively.

![Image source: InOncology](image.png)
Pembrolizumab improves progression-free survival vs. chemotherapy in first-line treatment of microsatellite instability-high advanced colorectal cancer
25 December 2020

Thierry André, MD, from the Sorbonne Université and Hôpital Saint Antoine, Paris, and colleagues recently reported results from the second interim analysis after average follow-up time of 32.4 months of the phase III KEYNOTE-177 trial. The findings continue to support the use of the immunotherapy drug pembrolizumab (Keytruda) as first-line treatment of patients with advanced microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer (CRC), demonstrating significantly prolonged survival outcomes compared to the standard of care fluorouracil (5-FU)-based chemotherapy.

Overview of the KEYNOTE-177 trial

307 patients from 23 different countries were randomly assigned between February 2016 and February 2018 to receive pembrolizumab or standard chemotherapy:

- either FOLFOX6 (5-FU, leucovorin, oxaliplatin) alone or combined with bevacizumab (Avastin) or cetuximab (Erbitux);
- FOLFIRI (5-FU, leucovorin, irinotecan) alone or combined with bevacizumab (Avastin) or cetuximab (Erbitux)

Treatment with pembrolizumab continued until the maximum dosage (35 doses of 200mg) or until disease progression, unacceptable toxicity, illness or physician or patient decision to withdraw from trial.

Average progression-free survival (the length of time during and after treatment that the patient lives with the disease but it does not worsen) among patients receiving pembrolizumab was double that of patients who received chemotherapy. Pembrolizumab was associated with fewer severe adverse events, and 36% of patients in the chemotherapy group had crossed over to receive pembrolizumab.

Take away message:

Long-term follow-up analysis of findings from the phase III KEYNOTE-177 trial supports the use of the immunotherapy drug pembrolizumab as initial therapy for patients with inoperable or metastatic MSI-H/dMMR CRC. Pembrolizumab led to significantly longer progression-free survival compared to chemotherapy when received as initial therapy, with patients experiencing fewer treatment-related toxicities.

READ THE FULL ARTICLE
Statins reduced risk of colorectal cancer in meta-analysis
10 December 2020

Findings from a recent study demonstrate that people who regularly took statins, a group of medicines that help to reduce low-density lipoprotein (LDL) “bad” cholesterol in the blood, had a significantly reduced risk of developing colorectal cancer (CRC). This chemoprotective effect was most pronounced among individuals who had inflammatory bowel disease, such as ulcerative colitis or Crohn’s disease, which are linked to an increased risk of developing CRC.

Lead investigator, Kevin Singh, MD, from NYU Langone Medical Center in New York City notes that “Chemoprotective agents to reduce the risk of colorectal cancer have been studied for decades”. While a large body of evidence shows that the most chemoprotective effect comes with daily, low-dose aspirin use, it is associated with an increased risk of gastrointestinal bleeding which compromises its usefulness as a chemoprotective agent.

Statins are the most frequently prescribed medications around the world and are generally well tolerated. Regular use of statins has been associated with risk reduction for several types of cancers, including breast, gastric and pancreatic.

The systematic meta-analysis evaluated findings from 52 different studies that involved more than 11 million individuals. Statin users had a 20% lower risk of developing CRC, while individuals with inflammatory bowel disease lowered their risk by about 60%. Further studies will be needed to confirm these findings, and examine whether the effects of statins varies according to the existing inflammatory condition.

Take home message:

Statins are the most frequently prescribed medications around the world, used to lower “bad” cholesterol levels in the body. A recent analysis found that statin use was associated with a significant 20% reduction in risk for colorectal cancer, and a 60% reduction in risk among individuals with inflammatory bowel diseases, such as Crohn’s disease or ulcerative colitis, which are known to increase one’s risk for developing colorectal cancer.
The use of Cytoreductive Surgery plus HIPEC in colorectal peritoneal carcinomatosis
15 December 2020

About 5% of colorectal cancer (CRC) patients have metastasis confined to the peritoneum (the lining of the abdominal cavity). Peritoneal carcinomatosis is a condition in which multiple cancers develop simultaneously in the peritoneum, usually after propagating from a primary source such as colorectal tumours. Up to now, no randomized controlled trial has established the independent benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) in CRC when added to cytoreductive surgery (CRS).

What is CRS-HIPEC?

It is a combination operation that consists of two separate procedures. It begins with surgical interventions of varying extent followed by heated chemotherapy drugs which are flushed though the abdominal cavity. CRS is always linked to HIPEC, as both treatments have been interconnected since their beginning. HIPEC has been popular in the treatment of peritoneal metastasis from CRC, despite being a highly heterogeneous treatment, which lacks uniformity across clinical practice.

How is CRS-HIPEC administered?

The first procedure is CRS. All gross, visible tumours in the peritoneum are removed, usually involving the surgical removal of affected organs, such as the colon, that have accumulated tumour deposits. After CRS, HIPEC is administered in order to remove any remaining cancer cells that could not be removed surgically.

During HIPEC, catheters are inserted into abdominal cavity to “wash” it with chemotherapy in a heated solution, which increases the ability of the drugs to kill cancer cells. Currently, there exists a great diversity of HIPEC protocols used worldwide, for example, involving different drugs and drug combinations, drug concentration, exposure time and temperatures. Uniformity across clinical practice is lacking and there remains a fundamental disagreement regarding the standardization of HIPEC protocols.

The PRODIGE 7 trial is the first randomized clinical trial to evaluate the effectiveness of CRS-HIPEC. In the study, patients were randomly assigned to receive CRS and HIPEC, while the other group received CRS alone. Through this approach, the trial investigators were able to assess the specific effect of HIPEC.

Findings from the study challenge the long-standing practice of HIPEC in peritoneal metastasis from CRC, where the addition of HIPEC with oxaliplatin was found to not influence overall survival outcomes. Complete CRS remains the mainstay of treatment, and should still be considered the standard of care in PM from CRC.
Currently, there is a crucial lack of peer-reviewed randomized controlled trial results that validate the effectiveness of HIPEC. Innovative modeling approaches may help to shed light on the reasons why it is not very effective and may lead to better alternatives and/or more rational approaches for the design of HIPEC procedures, such as exposure time or temperature.

**Take home message:**

Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is a therapy used for the treatment of peritoneal metastasis (PM) from colorectal cancer (CRC). There has been disagreement on the effectiveness of HIPEC within this multimodal approach. Findings from the PRODIGE 7 trial showed that the addition of HIPEC with oxaliplatin to CRS did not influence overall survival outcomes. Complete CRS remains the mainstay of this treatment, and should still be considered the standard of care in PM from CRC.

Hepatic Artery Infusion pumps in patients with colorectal cancer with liver metastases
22 December 2020

Hepatic Artery Infusion (HAI) chemotherapy is sometimes used as *adjuvant* treatment (treatment that follows the primary treatment to increase its effectiveness) in combination with systemic chemotherapy for the treatment of colorectal liver metastases (LM).
The Hepatic Artery Infusion (HAI) involves the continuous infusion of chemotherapy drugs directly into the liver from a pump that is inserted just below the skin. A catheter leaves the pump and is surgically connected to a branch of the hepatic artery.

In colorectal cancer (CRC), the liver is the most common site of metastasis. About 50% of patients with CRC develop LM in the course of their disease, and surgical resection remains the only treatment that offers a chance of cure and long-term survival (Chow, 2019). Only a minority of patients, however, is eligible for upfront surgery. HAI can be used in combination with systemic chemotherapy in the following instances:

- Among most patients who have LM that are considered inoperable, HAI can reduce tumour size and increase the likelihood of surgical removal of LM – about a third of patients so treated will become resectable;
- Among patients with resectable liver tumours, HAI can be used to reduce the chance of tumour recurrence.

A recent retrospective study showed that adjuvant HAI offered an increased overall survival, better response rates to treatment, and improved physical functioning compared to systemic chemotherapy alone (Kemeny, 2017).

How does HAI work?

HAI takes advantage of the fact that LM receive their blood supply from the artery that feeds the liver – the hepatic artery. While the liver receives blood flow from two different sources, one third from the hepatic artery and two thirds from the portal vein, CRC LM receive blood *exclusively* from the hepatic artery.
Beginning in the 1970s, chemotherapy was directly infused into the liver via the hepatic artery, allowing for higher concentrations of chemotherapy to be administered directly to the liver without causing high levels of toxicity to the rest of the body. Ongoing studies continue to examine the survival outcomes of HAI and any additional benefits it may offer in comparison to systemic chemotherapy. Despite the dramatic responses that HAI can offer, it remains a highly specialized technique that requires unique expertise, limiting its use to specific centres only.

**Take home message:**

Hepatic arterial infusion (HAI) is a treatment option for patients with colorectal cancer liver metastases that allows for a higher concentration of chemotherapy to be directly administered to the liver without causing high levels of toxicity to the rest of the body. HAI may be used to prevent tumour recurrence in the liver after surgery, or to help shrink liver metastases to increase the chances that they can be surgically removed.


Kemeny, N. et al. Updated long-term survival for patients with metastatic colorectal cancer
treated with liver resection followed by hepatic arterial infusion and systemic chemotherapy. J Surg Oncol. Author manuscript; available 2017 Apr 1. doi: 10.1002/jso.24189