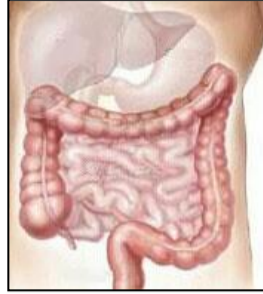


COLORECTAL CANCER RESEARCH UPDATES

Month Ending October 14th, 2011



The following colorectal cancer research update extends from September 17th, 2011 – October 14th, 2011 inclusive and is intended for informational purposes only.

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1. Chemo for the Conversion of Unresectable Colorectal Cancer Liver Mets to Resection (Sept. 28/11)

Resection (or surgical removal) of colorectal liver metastases (CLM) is the ultimate aim of treatment strategies in most patients with liver-confined metastatic colorectal cancer. Long-term survival is possible in selected patients with initially resectable or unresectable CLM. As a majority of patients have unresectable liver disease at the outset, the authors of this study claim there is a clear role for chemotherapy to downstage liver disease making resection possible. Studies of systemic chemotherapy with or without biologic therapy in patients with unresectable CLM have resulted in increased response rates, liver resection rates and survival. The authors maintain there is a sound physiologic rationale that exists for the use of hepatic arterial infusion (HAI) therapy (please see below for a description). Studies have shown that HAI with floxuridine combined with systemic chemotherapy increases response rates and liver resection rates in those patients with initially unresectable CLM. Toxicity from preoperative chemotherapy, biologic therapy and HAI therapy may adversely affect hepatic resection but the authors maintain can be kept minimal with appropriate monitoring. And finally, the authors maintain that all conversion strategies should be decided by a multidisciplinary team.

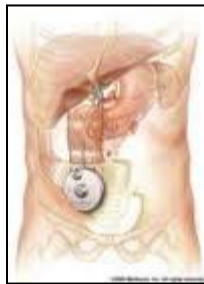
Hepatic Arterial Infusion (HAI):

HAI chemotherapy is designed to improve chemotherapy benefits for liver cancer by increasing the amount of chemotherapy delivered to the site of the tumor. Chemotherapy is dispensed from a specialized infusion system in which a catheter is placed into the hepatic artery to directly deliver the chemotherapy to the liver. A fully implanted system is used so that the pump that connects to the catheter in the hepatic artery is implanted under the skin. This allows for long-term administration of chemotherapy medication directly into the liver. The pump is periodically filled with chemotherapy by the oncologist.

Direct infusion of chemotherapy into the liver minimizes the side-effects of the chemotherapy and allows high doses to be administered. Infusion of chemotherapy directly into the hepatic artery (HA) to minimize the side effects of the chemotherapy is an option in selected patients with liver cancer or metastatic spread of cancer to the liver.

This treatment has been of special interest in patients with colorectal cancer with liver metastasis. Because liver metastases from colorectal cancer derive more than 80% of their blood supply from the hepatic artery, hepatic arterial infusion may be well suited as an alternative or together with systemic chemotherapy for the treatment of liver tumors. Hepatic artery infusion of chemotherapy has also been used in patients after liver resection (removal) for colorectal cancer spread to the liver.

(<http://www.surgery.usc.edu/divisions/tumor/pancreas/diseases/web%20pages/laparoscopic%20liver%20surgery/HAI.html>)



Please note: This procedure is not yet approved in Canada and can only be accessed in the U.S. through a trial setting.

Kemeny, NE, et al., Chemotherapy for the conversion of unresectable colorectal cancer liver metastases to resection. Crit Rev Oncol Hematol. 2011 Sept. 1; 79(3): 251-264.

2. More Evidence to Support VEGF Blocker Zaltrap (Sept. 29/11)

Patients who've undergone treatment for metastatic colorectal cancer had "statistically significant and clinically meaningful" improvement in survival when also given a multitargeted angiogenesis inhibitor, investigators reported here. The addition of aflibercept (VEGF Trap, Zaltrap) to standard chemotherapy was associated with about a six-week improvement in overall survival and a two-month increase in progression-free survival compared with chemotherapy alone. Patients with and without prior exposure to bevacizumab (Avastin) benefited from treatment with aflibercept, Josep Tabernero, MD, reported here at the European Multidisciplinary Cancer Congress, formerly known as the Congress of the European Cancer Organization and the European Society for Medical Oncology. Prior treatment with bevacizumab does not appear to significantly impact the safety profile of aflibercept." Aflibercept is a fusion protein consisting of the key domains of vascular endothelial growth factor (VEGF) receptors 1 and 2 and human IgG Fc. The compound blocks all isoforms of VEGF-A and VEGF-B, as well as placental growth factor. Tabernero reported findings from a multinational randomized trial involving 1,200 patients with metastatic colorectal cancer that had progressed on first-line treatment. All patients received FOLFIRI chemotherapy and were randomized to aflibercept or placebo. About 30% of patients had prior exposure to bevacizumab. After a median follow-up of 22.28 months, patients in the aflibercept arm had a median overall survival of 13.5 months versus 12.06 months for the placebo group, representing an 18% reduction in the hazard ratio (P=0.0032). Median progression-free survival was 6.9 months with aflibercept compared with 4.67 months with placebo, a 24% reduction in the hazard ratio (P=0.00007).

Tabernero, J, et al., Results from VELOUR, a phase III study of aflibercept versus placebo in combination with folfiri for the treatment of patients with previously treated metastatic colorectal cancer ECCO-ESMO 2011; Abstract LBA6.

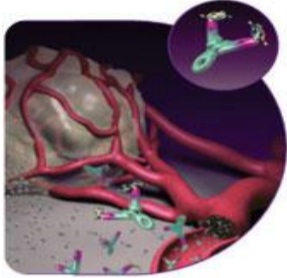
3. Administering Avastin Beyond Progression Improves Overall Survival in Metastatic Colorectal Cancer Patients (Sept. 29/11)

The results of this study show that patients with metastatic colorectal cancer, treated in a community setting with bevacizumab (avastin) beyond progression, experienced improved overall survival. These findings are consistent with similar studies, such as BRiTE and ARIES, which are two large registry trials showing extended survival with similar results. This study involved medical oncologists from across the country and evaluated data from as far back as 2004 using McKesson Specialty Health's electronic health record (EHR) system, iKnowMed. iKnowMed contains more than 975,000 patient records and is used by nearly 1,000 independent providers in community-based cancer care settings across the United States.

ABOUT AVASTIN (BEVACIZUMAB)

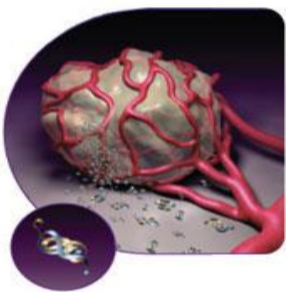
WHAT IS AVASTIN?

Avastin is currently approved as a treatment for metastatic colorectal cancer. This means that cancer cells have spread from the original site in the colon or rectum to another part of the body (most often the liver and or lungs). Avastin is not a chemotherapy but a class of agents known either as a biological therapy. More specifically they are a group of large proteins called **monoclonal antibody (Mab)**. These agents are similar to the antibodies the body's own immune system normally makes when we have a bacterial or viral infection but in this case it has been made in a laboratory and attacks specific targets on cancer cells. In the case of Avastin the target (otherwise called the antigen) is a protein called **Vascular Endothelial Growth Factor (VEGF)**. Avastin binds to VEGF, rendering it unable to then bind with its receptor which in turn by blocking the formation of new blood vessels then interferes with the growth of the tumour (see below).



HOW DOES AVASTIN WORK?

When cancer cells spread to another part of the body they try to form a lump or tumour mass. In order to do this, they need to rapidly stimulate the local blood vessels and capillaries to grow into the tumour mass in order to nourish the cancer cells with food and oxygen (a process called angiogenesis). They achieve this by releasing a chemical into the surrounding tissues called **Vascular Endothelial Growth Factor** (see adjacent picture). Avastin, being a monoclonal antibody which attaches to circulating VEGF, effectively blocks its ability to bind to its receptors in the tissues of the body, most importantly those surrounding tumours. Avastin, therefore, interferes with the tumour's ability to recruit new blood vessels reducing their ability to grow and spread to other areas of the body. As this process is universal to most bowel tumours, there is no requirement to perform extra laboratory tests on the cancer cells prior to Avastin therapy. There is also evidence that Avastin enhances the effect of chemotherapy. It is thought they make tumour vessels less "leaky" and so allows chemotherapy to reach the tumour more effectively.



Source: <http://www.cancernet.co.uk/avastin.htm>

<http://www.marketwatch.com/story/study-by-ocala-oncologythe-us-oncology-network-shows-use-of-bevacizumab-beyond-progression-in-metastatic-colorectal-cancer-patients-improves-overall-survival-2011-09-28>

4. Nerve Degeneration Detected Due to Oxaliplatin Effects (Sept. 28/11)

Oxaliplatin, a platinum-based anticancer drug that's made enormous headway in recent years against colorectal cancer, appears to cause nerve damage that may be permanent and worsens even months after treatment ends. The chemotherapy side effect, described by Johns Hopkins researchers, was discovered in what is believed to be the first effort to track oxaliplatin-based nerve damage through relatively cheap and easy punch skin biopsies. The Johns Hopkins investigators emphasize that the drug therapy clearly improves length of survival in advanced cancer by months to years, and that the goal of their new study is to find ways of preventing or slowing the damage through nerve-protective therapies identified through simple skin testing. Many patients who take oxaliplatin report bothersome neurological side effects, including pain in the hands and feet and numbness or tingling in the throat that affects swallowing. Though these symptoms develop over time in the majority of patients, some report neuropathies as early as when the drug is first infused. To get a better sense of how oxaliplatin affects nerve cells, researchers recruited eight cancer patients about to begin oxaliplatin treatment at The Johns Hopkins Hospital. All had been diagnosed with advanced colon cancer. Before their first oxaliplatin infusion, each patient underwent a comprehensive neurological examination, including nerve conduction testing, a clinical exam to look for signs of nerve damage, and a punch biopsy that removed tiny (3-mm diameter) portions of skin near their knees and ankles. Once oxaliplatin treatment began, consisting of infusions over two days once every two weeks for 12 cycles, the researchers performed the same tests after 30, 90 and 180 days. Another 180 days after they finished with treatment, the patients received one final exam. Test results showed that each of the patients' nerve function and neuropathy symptoms worsened over time and that results from the punch skin biopsies neatly mirrored the side effect arc. Using a microscope, the researchers saw that nerve cells' long extensions, called axons, degenerated over the course of oxaliplatin therapy. This progression persisted after treatment stopped. Even 180 days after their last doses, seven out of the eight patients' axons continued to wither. "This drug has rapidly

become the standard of care for people with advanced colon cancer, but we really knew little about how oxaliplatin affects nerves over time," the authors say. "With people living longer lives on oxaliplatin, it's important to know more about these neurological side effects so patients and their physicians can make educated choices on how this drug is used, and perhaps suggest ways to limit the damage." The new study strongly suggests that punch skin biopsies could be an easy and inexpensive way to follow nerve cell degeneration, a crucial prerequisite for testing the effectiveness of drugs currently in development to trace, prevent or slow nerve damage. "Skin biopsies can be done pretty easily, uniformly and cheaply anywhere, including hospitals, doctors' offices and clinics, and those places can have the tissue sent to Hopkins for analysis," the lead investigator Polydefkis says. "High-quality neurological testing isn't nearly as easy or economical to do, so it's possible that the biopsies could play a pivotal role in bringing neuroprotective drugs to fruition."

Polydefkis, M., et al., Longitudinal assessment of oxaliplatin-induced neuropathy. Neurology, 2011; 77 (10): 980 DOI: [10.1212/WNL.0b013e31822cfc59](https://doi.org/10.1212/WNL.0b013e31822cfc59)

5. **Colon Cancer's Spread to The Liver Blocked by Soy Peptide/Chemo Combo** (Sept. 29/11)

A new study reports a promising new weapon in treating metastatic colon cancer, particularly in patients who have developed resistance to chemotherapy. It has found that the soy peptide lunasin binds to a specific receptor in highly metastatic colon cancer cells, preventing them from attaching to the liver. "When lunasin was used in combination with the chemotherapy drug oxaliplatin, we saw a sixfold reduction in the number of new tumor sites," said de Mejia, the study author. In a separate study, the scientists showed that lunasin induces cell death in highly metastatic human colon cancer cells. Almost all colon cancer deaths are caused when cancer metastasizes -- or spreads -- to the liver. Until now chemotherapy has targeted the primary tumor because the process of metastasis is not well understood. "In this study, we have learned that lunasin can penetrate the cancer cell, cause cell death, and interact with at least one type of receptor in a cell that is ready to metastasize," said Vermont P. Dia, another study author. When that receptor is blocked, new blood vessels can't form and differentiate, and that prevents cancer from spreading. Binding such receptors has emerged as a promising target for developing cancer therapies. In the study, which mimicked the spread of colon cancer in humans, mice were separated into four groups:

- a control group;
- a group that was injected daily with lunasin;
- a group injected with the chemo drug oxaliplatin; and
- a group that received both lunasin and oxaliplatin.

After 28 days, the mice were examined to learn the extent of cancer's involvement in the liver. "The group that received lunasin alone had 50 percent fewer metastatic sites. But an even more exciting result was seen in the group that received both lunasin and the chemotherapy drug -- only 5 new cancer sites when compared with 28 in the control group," de Mejia noted. "This huge reduction in metastasis was achieved with the amount of lunasin in only 25 daily grams of soy protein, the amount recommended in the FDA health claim," Dia noted. The researchers said they recently analyzed commercial soy milks available in their area, and all contained lunasin. However, the amount of lunasin depended on the type of soy product that was used to prepare the soy milk. "Two glasses of soy milk a day generally provide half the amount of lunasin used in the study," said de Mejia. "It certainly seems feasible to create a lunasin-enriched product that people could consume in a preventive way." The scientists said their next step will be a colon cancer study in which they make lunasin part of the animals' diet -- rather than injecting the peptide -- to see if digestion and absorption alter its effectiveness. Soon they hope to be able to move on to human trials.

Gonzalez de Mejia, Elvira, et al., Lunasin Potentiates the Effect of Oxaliplatin Preventing Outgrowth of Colon Cancer Metastasis, Binds to $\alpha 5\beta 1$ Integrin and Suppresses FAK/ERK/NF- κ B Signaling. Cancer Letters, 2011; DOI: [10.1016/j.canlet.2011.09.002](https://doi.org/10.1016/j.canlet.2011.09.002)

Gonzalez de Mejia, Elvira, et al. Lunasin induces apoptosis and modifies the expression of genes associated with extracellular matrix and cell adhesion in human metastatic colon cancer cells. Molecular Nutrition & Food Research, 2011; 55 (4): 623 DOI: [10.1002/mnfr.201000419](https://doi.org/10.1002/mnfr.201000419)

6. **TAS-102 Makes Headway in Refractory Colorectal Cancer** (Sept. 29/11)

According to the results of this study, the experimental agent **TAS-102** significantly reduced the risk of death in a placebo-controlled phase II trial of patients with metastatic colorectal cancer refractory to current treatments. Patients receiving oral TAS-102 plus best supportive care had a median overall survival of 9 months, compared with 6.6 months for placebo and best supportive care. TAS-102 also doubled median progression-free survival (time before the disease got worse) from 1 month to 2 months. KRAS mutation testing revealed that TAS-102 offers a significant survival advantage for patients harboring a KRAS mutation, a biomarker of non-responsiveness to the approved targeted agents cetuximab (Erbix) and panitumumab (Vectibix). KRAS mutation-positive patients treated with TAS-102 had a median overall survival of 13.0 months, compared with 6.9 months for placebo, and a progression-free survival of 2.8 months vs. 1.0 month. A phase III trial is needed to confirm the promising results, but that "TAS-102 is the first cytotoxic agent to prolong survival in patients with metastatic colorectal cancer refractory to conventional cytotoxic agents." Researchers at 10 Japanese centers recruited 172 patients with refractory metastatic colorectal cancer after at least two lines of chemotherapy containing fluoropyrimidine, irinotecan, and oxaliplatin. Prior treatment also included

cetuximab in two-thirds and bevacizumab (Avastin) in at least three-fourths of the population. Patients were randomized double-blind 2:1 to best supportive care plus placebo or TAS-102 twice daily on days 1-5 and days 8-12 every 4 weeks. Among 169 evaluable patients, the disease control rate was 43.8% with TAS-102 vs. 10.5% with placebo.

<http://www.oncologyreport.com/news/clinical/single-article/novel-drug-tas-102-makes-headway-in-refractory-colorectal-cancer/baf9bff605.html>

7. **BINF 1120 Deemed As Effective as Avastin And With Fewer Side Effects** (Sept. 30/11)

In a randomized two arm phase II study which consisted of 126 patients, the medium progression-free survival (time before the disease got worse) of 10.6 months for individuals with metastatic colorectal cancer receiving **BIBF 1120** (afatinib) as initial treatment in conjunction with mFOLFOX6 was the same as those on bevacizumab (avastin) in combination with mFOLFOX6. Of note, just 34.1% of participants on BIBF 1120 reported serious side effects, compared to 53.7% of those taking bevacizumab. More detailed results from the trial are:

- 61.2% in the BIBF 1120 had an objective response, compared to 53.7% in the bevacizumab group
- Those in the BIBF 1120 group had almost the same progression-free survival rate at 9 months as the patients on bevacizumab (63% and 69%)
- Individuals in the BIBF 1120 group reported fewer serious gastrointestinal side effects (11.8%) in comparison to those receiving bevacizumab (29.3%)

As opposed to other angiokinase inhibitors which target just one receptor, BIBF 1120, a new type of triple angiokinase inhibitor, blocks three growth factor receptors simultaneously (VEGFR 1-3, PDGFR alpha and beta and FGFR 1-3). These receptor types are vital for angiogenesis - the formation and maintenance of new blood vessels. All three receptor types play a key role in the development and maintenance of new blood vessels (angiogenesis) for the tumour. The drug's inhibitory effect should undermine the possibility of angiogenesis, and may eventually stop tumor growth and spread. Prof Eric Van Cutsem, lead investigator for the trial, explained: *"These new study results hold promise for further investigation of BIBF 1120 in patients suffering from advanced colorectal carcinoma. It is utterly important to provide therapeutic options to our patients with less serious treatment complications, which is particularly significant as these patients have advanced disease. I would very much look forward to seeing further results to confirm the potential of BIBF 1120 in this patient population."*

Van Cutsem, E., A phase I/II open label, randomized study of BIBF 1120 plus mfolfox6 compared to bevacizumab plus mfolfox 6 in patients with metastatic colorectal cancer. ECCO-ESMO 2011, Abstract: 14LBA

8. **Perifosine Plus Capecitabine (Xeloda) As Second or Third Line Therapy** (Sept.29/11)

In this phase II trial, researchers compared the efficacy and safety of perifosine plus capecitabine (P-CAP) with placebo plus capecitabine (CAP) in patients with metastatic colorectal cancer who had progressed after as many as two prior therapies. 38 Patients not previously treated with capecitabine (also known as xeloda) received P-CAP or CAP in 21-day cycles until disease progression. The primary end point was time to progression (TTP – time till disease got worse). Secondary end points included overall survival (OS), overall response rate (ORR), safety, and tolerability. Twenty patients were randomly assigned to P-CAP and 18 to CAP. These were the following results:

- Median TTP (27.5 v 10.1 weeks);
- Median OS (17.7 v 7.6 months) were improved in patients receiving P-CAP versus CAP;
- ORR was 20% v 7% in the P-CAP and CAP groups, respectively, and one patient in the P-CAP group had a complete response;
- Toxicities, including diarrhea, nausea, fatigue, and hand-foot syndrome, were manageable.

Researchers concluded that P-CAP showed promising clinical activity compared with CAP in previously treated patients with metastatic colorectal cancer. A phase III trial is underway comparing P-CAP with CAP in patients with refractory mCRC.

Bendell, Johanna, et al., Randomized placebo-controlled phase II trial of perifosine plus capecitabine as second or third line therapy in patients with metastatic colorectal cancer. J of Clin Onc. Doi: 10.1200/JCO.2011.36.1980

9. **Administering Vectibix in First or Second Line Therapy** (Oct. 13/11)

Panitumumab (also known as vectibix) in combination with chemotherapy was evaluated in two pivotal clinical trials in first- and second-line treatment of metastatic colorectal cancer (mCRC), respectively. This study compared the health-related quality of life (HRQoL) of patients with or without panitumumab in the two trials. Patients with mCRC were randomized to FOLFOX (first-line trial) or FOLFIRI (second-line trial) ± panitumumab. In the first-line trial, 576 patients with wild-type KRAS mCRC (284 panitumumab + FOLFOX4 and 292 FOLFOX4 alone) were included in the HRQoL analyses. In the second-line trial, 530 patients with wild-type KRAS mCRC were included in these analyses (263 panitumumab + FOLFIRI and 267 FOLFIRI alone). After careful evaluation, study investigators concluded that the addition of

panitumumab to FOLFOX4 or FOLFIRI in first- or second-line treatment of wild-type KRAS mCRC significantly improved progression-free survival without compromising HRQoL.

Bennett, L., et al., health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first or second line treatment. British J of Cancer. October 11, 2011. Doi: 10.1038/bjc.2011.409.

10. **Defective Mismatch Repair Status As a Prognostic Biomarker of Disease Free Survival in Stage III Patients Treated with Adjuvant Folfox** (Oct. 14/11)

Adding oxaliplatin to adjuvant (post surgical) 5-fluorouracil (5FU) chemotherapy improves 3-year disease-free survival (DFS) after resection of stage III colon cancer. Several studies suggest that patients with tumors exhibiting **defective mismatch repair** (MMR) do not benefit from adjuvant 5FU chemotherapy, but there are few data on 5FU-oxaliplatin (FOLFOX) adjuvant chemotherapy in this setting. The aim of this study was to evaluate the prognostic value of **MMR status for DFS in patients with stage III colon cancer receiving adjuvant FOLFOX chemotherapy**. MMR status was determined by MSI testing or immunohistochemistry in 303 unselected patients with stage III colon cancer receiving adjuvant FOLFOX chemotherapy in nine centers. The 3-year DFS rate was significantly higher in the 34 patients (11.2% of the study population) with defective MMR tumors (90.5%) than in patients with proficient MMR tumors (73.8%). Researchers concluded that MMR status is an independent prognostic biomarker for DFS in stage III colon cancer patients receiving adjuvant FOLFOX chemotherapy.

What is DNA Mismatch Repair Status?

DNA Mismatch Repair Status refers to the system within the cell responsible for correcting errors resulting in DNA after it has replicated (or been copied), that works by detecting and replacing bases in the DNA that are wrongly paired (mismatched bases). The system repairs the mismatch. Tumours are either classified as either MMR deficient or defective (loss of tumour mismatch repair function) or MMR proficient (possessing tumour mismatch repair function).

Zaanan, Aziz, et al., Defective mismatch repair status as a prognostic biomarker of disease free survival in stage III colon cancer patients treated with adjuvant folfox chemotherapy. Clin Cancer Res. Published online first October 13, 2011. Doi: 10.1158/1078-0432.CCR-11-1048

SURGERY

11. **Comparing Surgery Alone, Radiotherapy, or Chemoradiotherapy in Advanced Rectal Cancer** (Sept. 27/11)

The aim of this study was to compare the results between surgery alone, preoperative radiotherapy (RT), or preoperative concurrent chemoradiotherapy (CCRT) followed by surgery in the treatment of locally advanced rectal cancer in Asian patients. The study included 151 patients with clinical T3, T4 or node-positive rectal cancer from Jan. 2005 to Dec. 2007.

- Eighty-six patients underwent total mesorectal excision (TME) alone or,
- 28 patients received preoperative RT followed by TME in 1 week, or
- 37 patients received preoperative CCRT followed by TME in 4-6 weeks.

Researchers found that the 3-year loco-regional recurrence (LRR), distant metastasis, overall and disease-free survival rates were comparable among Surgery, RT and CCRT groups. However, after reviewing the results, researchers concluded that preoperative RT or CCRT followed by TME produced good local control in favorable and unfavorable patients with locally advanced rectal cancer. If preoperative RT or CCRT is not given, **TME alone has a high incidence of local recurrence in unfavorable patients with 2 or more risk factors.**

Yeh, Chung Uhng, et al., Comparison of treatment results between surgery alone, preoperative short-course radiotherapy, or long course concurrent chemoradiotherapy in locally advanced rectal cancer. International J of Clin Onc. Doi: 10.1007/s10147.011.0317.0

12. **Chemo Plus Radiation Before Surgery Increases Tumor Response For Rectal Cancer** (Sept. 28/11)

Rectal cancer patients who use a new combination of the chemotherapy, Capecitabine (xeloda), together with five weeks of radiation (50 Gy) before surgery have an 88% chance of surviving the cancer three years after treatment, according to the results of a randomized trial. The results of the trial can recommend a new pre-operative treatment, the 'CAP 50' regimen, in locally advanced rectal cancer. It's safe and reduces the risk of the cancer coming back to less than 5%. The primary treatment for cancer of the rectum (found in the lower 15 centimeters of the bowel) is surgery. However, there is a risk of cancer re-growth within the bowel and surrounding tissues. Not only is this recurrence incurable in the majority of patients, but it can cause negative side effects. Depending on the location and stage of the

cancer, doctors usually recommend radiation therapy and chemotherapy before surgery. The optimal regimen is still in discussion. The ACCORD 12 trial involved 598 patients with locally advanced rectal cancer (tumors that have spread to the perirectal fat, but not travelled to distant parts of the body) who were diagnosed and treated in 50 hospitals in France between 2005 and 2008. Researchers wanted to find the most effective and safe preoperative treatment for rectal cancer by comparing a combination of two different chemotherapies and two different radiation doses. Patients were randomized to receive either

- Cap45 (chemotherapy, Capecitabine, and radiation treatment at 45 Gy) or
- Capox50 (chemotherapies, Capecitabine and Oxaliplatin, along with radiation at 50 Gy).

At three years after treatment, the Capox50 regimen did not significantly increase the chance of the cancer returning or surviving the disease, compared to the Cap45 treatment. Oxaliplatin, given as part of the Capox50 treatment, was shown to immediately increase side effects, with some cases of severe diarrhea, and was not effective in increasing the chance of local tumor sterilization. However, the increase of radiation dose from 45 to 50 Gy in five weeks was effective, well tolerated and did not extend the duration of treatment. "The results of this trial, when analyzed together with the Italian STAR01 and the American NSABP R04 randomized trials, bring solid scientific evidence that a 'CAP50 regimen' should be the standard treatment for locally advanced rectal cancer. Using Capecitabine avoids the intravenous injection of fluorouracil, while a radiation dose of 50 Gy in 25 fractions over five weeks increases the chance of tumor sterilization and limits the risk of local recurrence to 5% or less," investigators claimed.

Jean Pierre Gerard, Accord12/0405-prodige 2 Phase III Trial Neoadjuvant Treatment in Rectal Cancer: Results After 3-Years of Follow-up," (abstract #3). American Society for Radiation Oncology.

13. **Resectability with Erbitux Extends Life** (Oct. 7/11)

Combining the epidermal growth factor receptor (EGFR) inhibitor cetuximab (better known as erbitux) with conventional chemotherapy improves survival in patients who have had complete resection of colorectal liver metastases that were initially judged to be unresectable, according to data presented at the 2011 European Multidisciplinary Cancer Congress (EMCC). Investigators randomized 110 patients to cetuximab plus FOLFOX6 (oxaliplatin, fluorouracil, and folinic acid) or cetuximab plus FOLFIRI (irinotecan, fluorouracil, and folinic acid). Patients were assessed for response every eight weeks by CT or MRI. A multidisciplinary team reassessed resectability after 16 weeks and then every two months for up to two years. At baseline, study participants had unresectable, histologically confirmed colorectal liver metastases with no extra-hepatic metastases. Individuals determined at follow-up to be resectable were offered liver surgery within four to six weeks of their last treatment cycle. KRAS status was retrospectively determined. The investigators conducted their analysis to determine whether complete resection increases long-term survival. A prior analysis of the study population showed an R0 (complete) resection rate of 34% in patients with KRAS wild-type tumors treated with cetuximab plus either of the two chemotherapy regimens. The new analysis found that the median overall survival (OS) was 33.1 months in the overall study population and 36.1 months in patients with KRAS wild-type tumors. When analyzed by R0 resection status, the median OS was 46.7 months in the R0-resected group versus 27.3 months in the group that was not R0-resected. The four-year survival rate was 49% in R0-resected patients versus 16% in non-R0-resected patients. Also, the two treatment regimens demonstrated similar progression free survival (PFS – time before the disease got worse) and OS. "The main message is that resectability after treatment with cetuximab and FOLFOX6 or FOLFIRI but not at baseline is associated with longer survival," Professor Folprecht said. He emphasized that despite favorable long-term survival, the median disease-free survival after R0-resection of about 10 months underscores the need for multidisciplinary cooperation and patient selection, especially in patients with a large number of metastases. The phase II Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases (CELIM) study was conducted at 17 sites in Germany and Austria.

<http://www.medicalnewstoday.com/articles/235670.php>

SCREENING

14. **Men Require Earlier Screenings** (Sept. 27/11)

A new study suggests men and women should be screened for colorectal cancer starting at different ages. The Austrian study found that men frequently have advanced polyps that could lead to colorectal cancer at ages 45 to 49, a decade earlier than women. These findings have prompted the researchers to conclude that men should likely have their first colonoscopy earlier than 50, the age that current guidelines recommend. The study, conducted across Austria between 2007 and 2010, included 44,350 people whose average age was 60. A nearly equal number of men and women participated in the study. Each of them underwent a colonoscopy, a procedure in which a tube-mounted video camera is inserted into the rectum and then snaked through the colon, where it is used to identify cancerous and potentially precancerous growths. Colonoscopies are considered the gold standard tests for detecting colorectal

cancer. Just over 60% of the study participants were given a clean bill of colon health -- no abnormalities were found. Among those whose exams revealed a type of precancerous polyp known as an adenoma, men were much more likely to develop them at a younger age than women. For example, 18.5% of men aged 50 to 54 had adenomas compared to 10.7% of women that age. It isn't until women are 65 to 69 years old that their likelihood of adenomas matches men in their early to mid 50s, the researchers note. According to the study, the likelihood that women have polyps increased as they entered their 60s. For men, a similar increase occurred when they were much younger, between the ages of 45 and 49. Men were also twice as likely as women to have advanced adenomas, growths that have greater potential to lead to cancer. Overall, men were twice as likely to be diagnosed with colorectal cancer.

Ferlitsch, Monika. Journal of the American Medical Association, Sept. 28, 2011; vol 306: pp 1352-1358.

OTHER

15. Bloodstream Infections Increased Risk for Colorectal Cancer (Sept. 21/11)

Patients who develop incident bloodstream infections are at increased risk for diagnosis of colorectal cancer within 1 year of infection. Bloodstream infections may be a marker for colorectal malignancy. Therefore, researchers set out to determine the overall and species-specific risk for colorectal cancer within 1 year after incident infection. Between 2000 and 2007, researchers conducted a population-based inception cohort design in adults in the Calgary Health Zone. Those with bloodstream infections were followed until development of colorectal cancer or mortality through 2008. A total of 10,121 bloodstream infections occurred among 8,806 patients with a mean age of 62.4 years; 54.5% were male. Colorectal cancer was diagnosed in 3,859 regional residents, of which 349 occurred after an incident bloodstream infection. Compared with the general population, 71 patients had colorectal cancer diagnosed concomitantly with or within 1 year after infection. *Clostridium*, *Bacteroides fragilis* and other anaerobes were significant risk factors for a new colorectal diagnosis, according to the researchers. In addition, male gender, age, and liver disease were significant risk factors. The researchers recommend "further research to define the role of colorectal cancer preventive or early diagnostic screening investigations in patients who present with bloodstream infections."

<http://www.hemonctoday.com/article.aspx?rid=87771>

16. Heart Protein May Be Target for Colon Cancer Therapy (Sept. 21/11)

A protein critical in heart development may play a part in colon cancer progression. Research led by investigators from Vanderbilt-Ingram Cancer Center and the Vanderbilt Eye Institute suggests that the protein BVES (blood vessel endocardial substance) -- which also is key in regulating corneal cells -- may be a therapeutic target for halting colon cancer metastasis. The study further suggests that BVES may be important more broadly in many, or most, epithelial cancers. About 85% of cancers originate in epithelial cells that form the body's external and internal linings (such as the skin and the lining of the gastrointestinal tract). However, the main clinical concern is not the primary tumor, but the potential for that tumor to leave its tissue of origin and spread throughout the body (a process called "metastasis"). A critical step in metastatic progression of epithelial cancers happens when epithelial cells "revert" to a less differentiated state -- a process called "epithelial-mesenchymal transition" or EMT. Investigators came together in this study to assess BVES expression in human colorectal cancers. They found that BVES levels were very low in all stages of colon cancer. They also noted decreased BVES levels in many other types of epithelial cancers (including breast) and in several colorectal cancer cell lines. To uncover why BVES levels were reduced, the investigators enlisted additional help from other investigators like Wael El-Rifai, M.D., Ph.D., and colleagues. They determined that the BVES promoter (a DNA region that controls gene expression) was heavily modified (methylated), which silenced its expression. In cell experiments, the researchers showed that treating cells with a "demethylating" agent (the drug decitabine, which is currently used to treat myelodysplastic disorders) restored BVES expression. When BVES was expressed in colorectal cancer cell lines, they became more epithelial in nature and their tumor-like characteristics (in cell experiments and in animal models) decreased. These findings suggest that treatment with agents to increase BVES levels might provide a way to decrease aggressive behaviors of colorectal and other epithelial cancers. "In cancer, typically the primary tumor doesn't kill you; it's the metastatic disease that proves lethal," claim the investigators. "So if targeting BVES could interfere with metastasis, that would be very exciting." The researchers also identified signaling pathways involved in BVES function that may represent other therapeutic targets -- and that revealed new insights into the normal biological function of BVES. The findings could have implications in wound healing and other normal functions of epithelial cells, as well as for many types of epithelial cancer. "We don't think it's just isolated to the colon; it pertains to a broad lot of epithelial cancers". "And that's a lot of cancers."

El-Rifai, Wael, et al. BVES regulates EMT in human corneal and colon cancer cells and is silenced via promoter methylation in human colorectal carcinoma. Journal of Clinical Investigation, 2011; DOI: [10.1172/JCI44228](https://doi.org/10.1172/JCI44228)

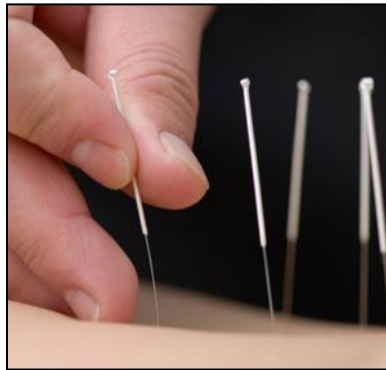
17. **Diabetes Increases Colorectal Cancer Risk** (Sept. 29/11)

According to the results of this study, people suffering from diabetes mellitus are at greater risk of contracting colorectal cancer. However, the investigators were not able to clearly state the reason for this connection nor have they predicted any remedy to treat or avoid this form of cancer. Researchers combined the results of 14 international studies and found that people with diabetes were 38% more likely to be diagnosed with colon cancer than those who were diabetes-free. They found that diabetes was associated with an increased risk of colon cancer in both men and women. However, the risk of rectal cancer was 20% higher in men. "This data suggests that diabetes mellitus is an independent risk factor for colon and rectal cancer," said Hiroki Yuhara, the lead researcher in the study. According to Yuhara, people with diabetes should be aware of the risk of contracting colon cancer and follow their doctor's advice and screen themselves for the cancer. The researchers have also recommended that the doctors be aware of an increased colorectal cancer risk in patients who smoke and are obese; more so, in fact, than the ones who have diabetes. While the findings state that diabetes has been associated with an increased risk of colorectal cancer, they do not prove that diabetes mellitus directly contributes to colon cancer in some people.

<http://www.ibtimes.com/articles/222159/20110929/diabetes-mellitus-colorectal-cancer-diabetes-university-of-california-colon-and-rectal-cancer.htm>

18. **Does Acupuncture Help Radiation-Induced Nausea?** (Oct. 1/11)

In this study, almost all patients felt they had less nausea after either real or sham acupuncture to manage nausea and vomiting during radiation therapy. Nine out of ten wanted more treatments. The sham procedure used non-penetrating needles just pressed against the skin, but neither the patients who received real acupuncture nor those who received sham treatments knew which they received.



Ninety-five percent in the real acupuncture group and 96 percent in the sham acupuncture group believed that the treatment had been effective against nausea. However, 70% of the real group and 62% of the sham group did experience nausea — for an average of 10 days for real treatments and 9 days for sham. In addition, 25% of the real group and 28% of the sham group vomited. So measured objectively, there was still significant nausea and whether or not acupuncture was “real” or just pretend, it made no measurable difference. Dr. Anna Enblom from the Karolinska Institute in Stockholm commented: *The beneficial effects seem not to come from the traditional acupuncture method, but probably from the patients' positive expectations and the extra care that the treatment entails.*

Enblom, Anna, et al., Acupuncture compared with placebo acupuncture in radiotherapy-induced nausea – a randomized controlled study. Annals of Oncology. First published online: September 23, 2011.

19. **Combination Therapies for Drug-Resistant Cancers** (Oct. 11/11)

Some cancers can be effectively treated with drugs inhibiting proteins known as receptor tyrosine kinases, but not those cancers caused by mutations in the KRAS gene. Colorectal cancer is one of those cancers. A team of researchers has now identified a potential way to effectively use receptor tyrosine kinases inhibitors to treat individuals with KRAS mutant colorectal cancers -- combine them with inhibitors of the MEK/ERK signaling pathway. In cases in which tyrosine kinase inhibitors are effective, they reduce signaling via both the PI3K/AKT and MEK/ERK signaling pathways. It is thought that KRAS mutant cancers, such as colorectal, are resistant to tyrosine kinase inhibitors because the mutant KRAS protein can directly activate ERK and PI3K signaling. However, Engelman and colleagues discovered that although mutant KRAS activates ERK signaling in human KRAS mutant colorectal cancers, receptor tyrosine kinases control PI3K signaling. Of potential clinical significance, treating mice xenografted to bear a human KRAS mutant colorectal cancer cell line with a combination of a receptor tyrosine kinase inhibitor and a MEK inhibitor induced **tumor regression**. These data suggest a way in which receptor tyrosine kinase inhibitors could be used to treat individuals with KRAS mutant colorectal cancers. However, the authors caution that heterogeneity among KRAS mutant cancers means that the approach would not work in all patients with such cancers. The results are promising but require further studies going forward.

20. Potential Biologic Therapies That Specifically Target Metastasis (Oct. 11/11)

Researchers from this study have shown that a protein can inhibit metastasis of colon and melanoma cancers. Chemokines and chemokine receptors are extensively involved in metastasis of 23 different forms of cancer. The chemokine referred to as CXCL12 is naturally expressed in the bone marrow, lungs and liver, all organs where cancer commonly metastasizes, but is often repressed in colon, breast and lung cancers. In previous studies, researchers from the Dwinell laboratory had shown CXCL12 to reduce tumor growth and metastasis in colon and breast cancers. In those experiments, CXCL12 was engineered to produce the protein. However, for this study, researchers administered wild-type CXCL12 (naturally occurring CXCL12) or different oligomeric structures, either “monomer” (single) CXCL12 or a “dimer,” a paired CXCL12 protein molecule and compared the results for both tumor growth and metastatic suppression. CXCL12 proteins effectively blocked metastasis of the colon cancer and dramatically improved survival time, with the dimer showing effectiveness in blocking melanoma metastasis as well. Together with their prior results, the laboratory has shown that repression of native CXCL12 expression is a key signature in colon cancer whose impact on tumor malignancy can be reversed by administering the chemokine proteins. They also demonstrated that the single or paired proteins blocked metastasis while initiating unique biochemical signals through the receptor CXCR4. “These data establish CXCL12 as a potential avenue for the next generation of biologic therapies that specifically target metastasis, which is key in cancer treatment and the improvement of survival rates” said Dr. Dwinell.

<http://www.medicalnewstoday.com/releases/235774.php>

NUTRITION & HEALTHY LIFESTYLE

21. Fruits & Vegetables & Colorectal Cancer Risk (Sept. 23/11)

According to the results of this study, a poor diet, specifically one that is skimpy on fruits and vegetables, is associated with an increased risk of colorectal cancer. While previous studies involving hearty produce consumption and colorectal cancer have had mixed results, the researchers in this study speculate that determining the specific location of the cancer may be an important factor as not all cancers in the bowel are created equal. According to the researchers, the genetic makeup and development of the types of cancer that typically are found in the **distal section (left side)** of the colon, the **proximal section (right side)** of the colon, and the **rectum (lower part)** appear to all be different, and thus, may respond differently to specific fruits and vegetables. The failure of past research to show that produce consumption protected against colorectal cancers may be due to the fact that the studies lumped all the cancers sites in the bowel area together. In this study of over 1,700 participants, the researchers uncovered that **cruciferous vegetables**, including Brussels sprouts, cabbage, cauliflower, and broccoli were associated with a reduced incidence of **proximal and distal cancers**. A diet abundant in both **fruits and vegetables**, especially apples and dark yellow vegetables, such as carrots and pumpkin, appeared to decrease the risk of **distal cancer**. Surprisingly, consuming more fruit juice appeared to *increase* the risk of rectal cancer. While more studies are needed to confirm these findings and uncover the possible mechanisms involved, tailoring future research according to the location of the cancer and specific types of fruits and vegetables consumed is food for scientific thought. Epidemiologist and study author Professor Lin Fritschi, PhD commented: *Fruits and vegetables have been examined extensively in nutritional research in relation to CRC, however, their protective effect has been subject to debate, possibly because of different effects on different subsites of the large bowel. It may be that some of the confusion about the relationship between diet and cancer risk is due to the fact that previous studies did not take site of the CRC into account. The replication of these findings in large prospective studies may help determine whether a higher intake of vegetables is a means for reducing the risk of distal CRC.*

Fritschi, Lin, et al., Fruit and vegetable consumption and the risk of proximal colon, distal colon, and rectal cancers in a case-control study in western Australia. J of the Amer Dietetic Assoc. Vol. 111, Issue 10, pp. 1479-1490.

22. Even Little Exercise Helps With Cancer (Sept. 21/11)

Although recommendations are for 150 minutes of exercise a week or 30 minutes a day to reduce risk of dying from cardiovascular disease or cancer, even less activity can increase life expectancy, according to the results of this study. Following over 415,000 people in Taiwan over an average of 9 years, researchers found that even 15 minutes a day (92 minutes a week) of physical activity increased life expectancy three years compared to those people who had no exercise at all.



The no exercise group had a 17% increased risk of dying compared to the low-exercise group. After an initial 15 minutes every day (low-volume exercise) every additional 15 minutes of daily exercise decreased risk of dying from any cause by 4% and dying from cancer by 1%.

Pang, Chi, et al., Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. The Lancet. Vol. 378, Issue 9798: pp. 1244-1253.

23. **Spicing Up Broccoli Boosts Cancer-Fighting Power** (Sept.21/11)

Teaming fresh broccoli with a spicy food that contains the enzyme myrosinase significantly enhances each food's individual cancer-fighting power and ensures that absorption takes place in the upper part of the digestive system where the maximum health benefit is received. To get this effect, spice up broccoli with mustard, horseradish, or wasabi. The spicier, the better.



In the study, when fresh broccoli sprouts were eaten with broccoli powder, the scientists were able to measure bioactive compounds in the blood 30 minutes later. When these peaked at three hours, they were much higher when the foods were eaten together than when either was eaten alone. Urine samples corroborated the blood results. It's no secret that many people cook the benefits right out of broccoli instead of steaming it lightly for two to four minutes to protect its healthful properties. "However, this study shows that even if broccoli is overcooked, you can still boost its benefits by pairing it with another food that contains myrosinase," claims the study's lead author. Myrosinase is the enzyme necessary to form sulforaphane, the vegetable's cancer-preventive component. Note what happened with the fresh broccoli sprouts and broccoli powder eaten in this experiment. The powder doesn't contain myrosinase, but it does contain the precursor to the anti-cancer agent sulforaphane. Eaten together, the sprouts were able to lend their myrosinase to the powder. As predicted, both foods produced sulforaphane and provided greater anti-cancer benefit. Other foods that will boost broccoli's benefits if they are paired together include radishes, cabbage, arugula, watercress, and Brussels sprouts. Another benefit of protecting and enhancing the myrosinase in foods: "If myrosinase is present, sulforaphane is released in the ileum, the first part of the digestive system. Absorption happens well and quickly there, which is why bioactivity is seen in 30 minutes." An earlier study showed that microbiota are capable of releasing sulforaphane in the lower gut, but absorption happens more slowly in the colon than in the upper intestine. Scientists say that as little as three to five servings of broccoli a week provide a cancer-protective benefit. But it pays to spice it up for added benefits and find ways to make it appealing so you don't mind eating it if you're not a broccoli fan.

Cramer, Margarita et al., Enhancing sulforaphane absorption and excretion in healthy men through the combined consumption of fresh broccoli sprouts and a glucoraphanin-rich powder. British Journal of Nutrition, 2011; 1 DOI: [10.1017/S0007114511004429](https://doi.org/10.1017/S0007114511004429)

24. **Calcium and Vitamin D may Reduce Risk of Colorectal Cancer** (Sept. 22/11)

A new study led by researchers at Memorial University shows that dietary calcium and vitamin D are associated with a lower risk of colorectal cancer. The study was based on the comparison of dietary information between colorectal cancer patients and controls collected from more than 4,000 participants in Newfoundland and Labrador and Ontario. Data for the study were obtained from the Newfoundland Familial Colorectal Cancer Registries and the Ontario Familial Colorectal Cancer Registries. Participants willing to participate in the study filled out a family history questionnaire, personal history questionnaire and food frequency questionnaire. Results of the study showed that overall, higher calcium and vitamin intake are associated with lower risk of colorectal cancer in both Newfoundland and Labrador, and Ontario. For people with low intake or calcium and vitamin intake from foods, supplements containing the two nutrients are associated with reduced risk of colorectal cancer. And although Newfoundland and Labrador has the highest incidence of colorectal cancer in Canada, people in Newfoundland and Labrador have lower calcium intake and eat less fruits and vegetables than their Ontario counterparts.

<http://www.med.mun.ca/Medicine/CommunicationsNews/NewsMedicine/September-2011/Calcium-and-vitamin-D-may-reduce-risk-of-colorecta.aspx>

25. **Ginger Supplements May Help Prevent Colon Cancer** (Oct. 13/11)

New research suggests a common spice, taken in supplement form, may reduce colon cancer risk. Researchers at the University of Michigan Medical School randomized 30 study participants to receive

either two grams of ginger root supplement or a placebo each day for 28 days. After this short period, researchers discovered that participants who took ginger reduced inflammation of the colon, which has been linked with the development of colon cancer, by a remarkable 28%. Lead researcher, Suzanna M. Zick, N.D., M.P.H., suggested further clinical research is necessary to determine if ginger actually fights cancer. "Interest in this is only going to increase as people look for ways to prevent cancer that are nontoxic, and improve their quality of life in a cost-effective way," she said. Ginger has been used as a medicine in Asia and India for thousands of years to treat stomach upset, diarrhea and nausea.



2 grams of ginger supplements daily may reduce colon cancer risk.

Source: <http://www.examiner.com/holistic-health-in-salt-lake-city/ginger-root-photo>

Zick, Suzanna, et al., Phase II Study of the Effects of Ginger Root Extract on Eicosanoids in Colon Mucosa in People at Normal Risk for Colorectal Cancer. Cancer Prevention Research. Published Online First October 11, 2011; doi: 10.1158/1940-6207.CAPR-11-0224