

COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH Month Ending March 12, 2009

The following colorectal cancer research update extends from February 7 – March 12, 2009 inclusive and is intended for informational purposes only.

DRUGS

1. **Study of Tegafur-Uracil/Leucovorin Combined with 5FU/Leucovorin and Irinotecan in Patients with Advanced Colorectal Cancer** (Feb. 7/09)

Folfiri (5FU + Leucovorin + Irinotecan) is a current standard of care therapy administered for advanced colorectal cancer either in the first or second line setting. Its administration, however, can be difficult because of the 2-day infusional 5FU component of folfiri. Therefore, the replacement of the 2-day-infusional 5FU of Folfiri with oral tegafur-uracil/leucovorin (UFT/LV) would be highly beneficial for clinical management and for patients, and a phase I trial was performed using oral UFT/LV. (Tegafur is taken up by cancer cells and breaks down into 5FU which kills tumor cells. Uracil causes higher amounts of 5FU to stay inside the cells so that they may be destroyed)

Treatment consisted of infusional irinotecan and a bolus injection of 5FU on day 1, and oral UFT on days 1-5, days 1-7 or days 1-10. Cycles were repeated every 14 days. There were a total of 19 patients enrolled, and based on toxicities experienced, it was determined that a 7 day administration of UFT/LV was recommended. A phase II study is ongoing to validate the clinical outcome.

Chayahara, Naoko et al., Phase I and Pharmacokinetic Study of Tegafur-Uracil/Leucovorin Combined with 5Fluorouracil/Leucovorin and Irinotecan in patients With Advanced Colorectal Cancer. American Journal of Clinical Oncology: Vol 32 (1) Feb 2009; pp 56-60

2. **FDA Approves Clinical Studies of a Novel Anti-Cancer Drug Developed by Italian Researchers** (Feb. 10/09)

Nerviano Medical Sciences has secured Food and Drug Administration approval to conduct for the first time clinical trials of a novel antitumoral agent. The drug is a Cdc7 inhibitor, which means it prevents the uncontrolled proliferation (growth) of cancer cells and it induces cell death by apoptosis (programmed cell death). The preclinical data, recently published in the prestigious journal Nature Chemical Biology

(www.nature.com/nchembio/journal/v4/n6/full/nchembio.90.html) demonstrate that inhibition of Cdc7 induces tumor cell death and blocks the growth of various types of cancer, including colon, in experimental animal models. The compound is efficacious on cancer cells of various origins, including those resistant to the tumour replication inhibitors already on the market. The FDA approval will allow conducting clinical phase I trials in cancer patients, including colorectal. Trials are set to commence within the next few months.

www.therapeuticsdaily.com/news/FDAApprovesClinicalStudiesofaNovelAnti-CancerDrugDevelopedbyItalianResearchers

3. **Long-Term Aspirin Use Seems to Protect Against Colorectal Lesions** (Feb. 10/09)

A study published in the February 18th issue of the Journal of the National Cancer Institute concluded that prolonged use of low-dose aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk of precancerous lesions that can lead to colorectal cancer. NSAID drugs interfere with the development of cancer in the large bowel. (Examples of NSAIDs include ibuprofen, naproxen, sulindac, indomethacin, celebrex, and aspirin.) This study showed 2 things:

- If you take NSAID drugs for a while and then stop, you won't get a big rebound in terms of adenoma tumor risk
- If you don't stop taking an NSAID, but instead continue its use over time, the protective benefit will continue.

This study focused on people who had embarked on long-term use of aspirin as part of the Aspirin/Folate Polyp Prevention Study. 1100 participants were considered at high risk for developing colorectal cancer because of a history of polyp development. The patients who took aspirin were 28% less likely to develop advanced adenomas than those taking a placebo and 17% less likely to develop any adenoma.

Cole, B et al., Aspirin for the Chemoprevention of Colorectal Adenomas: meta-analysis of the randomized trials. J of National Cancer Institute 2009; 101: 256-266

4. **Erbix Plus Folfox6 or Erbitux Plus Folfiri as Neoadjuvant Treatment of NonResectable Colorectal Liver Mets (CELIM-Study)** (Feb. 12/09)

With the use of highly effective chemotherapy regimens with high response rates, initially non-resectable liver mets can be converted to resectable liver mets, thereby offering potentially curative treatment. Therapies containing erbitux have demonstrated high response rates in previous studies. In this phase II study, patients with non-resectable liver mets were randomized to receive folfox6 plus erbitux **or** folfiri plus erbitux. The resection rate for erbitux + folfox6 was 40% and the resection rate for erbitux + folfiri was 43%. Investigators concluded that the combination of erbitux with standard chemotherapy demonstrated high activity in Kras wild type patients and an encouraging rate of liver resection.

Folprecht, G, et al., Cetuximab Plus Folfox6 or Cetuximab Plus Folfiri as Neoadjuvant Treatment of Nonresectable Colorectal Liver Metastases: A randomized Multicenter Study (CELIM study). Abstract 296. ASCO 2009 GI Symposium.

5. **High Blood Pressure May be A Marker for Avastin Outcome** (Feb. 13/09)

Hypertension (High Blood Pressure) may be a marker for avastin outcomes. 39 patients were studied for the treatment of colorectal cancer using first line therapy with avastin in this study. 20% (8 patients) developed moderate to severe hypertension during treatment. Six of those eight had a partial cancer remission, while only 10 of those who didn't have high blood pressure had tumor shrinkage. The progression free interval (the time wherein the cancer did not get worse) for patients with hypertension was 14.5 months compared to 3.1 months for those without the side effect.

Scartozzi, M. et al., Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Annals of Oncology: 2009; 20(2): 227-230

6. **Biocompatibles Treats First Patient In Drug-Eluting Beads Trial On Colorectal Cancer Metastases** (Feb. 17/09)

Biocompatibles International PLC has treated the first patient in a clinical trial for the evaluation of Drug Eluting Beads, delivering irinotecan (DEBIRI) for the treatment of liver mets from colorectal cancer, in a trial known as Paragon II. Paragon II is a British phase II study evaluating DEBIRI in patients who are eligible for surgery to remove tumours. 20 patients will be treated – initially with debiri and then, approximately one month later, by surgery. The drug eluting bead treatment appears to be well tolerated. A study in Louisville, Kentucky recently furnished the results from a group of 55 patients with liver mets from colorectal cancer, who had been treated with debiri as well. The 6 month response rate was 66% compared with a benchmark of 12%, and the authors concluded that the treatment was “safe and effective in the treatment of metastatic colorectal cancer..”

www.proactiveinvestors.co.uk/companies/news/4460/biocompatibles-treats-1st-patient-in-drug-eluting-beads-trial-on-colorectal-cancer-metastases-4460.html?BII

7. **New Drug in Clinical Development (Enzastaurin) May Be Able to Prevent Colon Cancer Development** (Feb. 13/09)

Researchers at the Mayo Clinic campus in Florida have found that a drug now being tested to treat a range of human cancers significantly inhibited *colon cancer* development in mice. Because the agent appears to have minimal side effects, it may represent an effective chemopreventive treatment in people at high risk for colon cancer. Their study found that use of the oral agent **enzastaurin** significantly reduced development of cancerous colon tumours in treated animals. Furthermore, the tumors that did develop in mice were of a lower grade, which meant they were less advanced and aggressive than the tumors seen in animals not given the drug. The lead investigator claimed that there is a need for an agent that has a proven ability to reduce colon cancer risk, and this study suggests that enzastaurin could be uniquely effective. Enzastaurin is a drug that targets a specific protein kinase in cells that can lead to abnormal cell division and growth, reducing colon cancer in mice. Protein kinases change the chemical structure of other proteins and the signals that they send within cells. Enzastaurin blocks protein kinase C-beta II, reducing changes to expression of three genes critical to the growth and

development of colon cancer. The drug is also being studied as a treatment for several other cancers, such as B-Cell lymphoma and high grade brain gliomas.

Murray, Nicole, et al., Protein Kinase C Beta Is an Effective Target for Chemoprevention of Colon Cancer. Cancer Research 69, 1643, February 15, 2009. doi: 10.1158/0008-5472.CAN-08-3187

8. Intense Combination Chemotherapy Enables Surgery for Initially Unresectable Colorectal Mets (Mar. 3/09)

Treated with a combination of 3 chemo drugs, 1 in 5 patients whose colorectal cancer had spread too far for surgery were able to have operations to remove metastatic tumors. After five years, a third of them were alive with no sign of cancer. Investigators in Italy treated 200 stage IV patients with a combination of 5FU, oxaliplatin, and irinotecan (folfoxiri) during three different clinical trials. While all three drugs are commonly used to treat colorectal cancer, they are not usually used at the same time. Initially, all of the patients had cancer that had spread beyond the possibility of having it removed surgically. After a median time of five and a half months, 20% of the patients were able to have surgery to completely remove all visible cancer (**Ro resection**). 5 years later nearly half (42%) were still alive and a third (33%) survived eight years. Almost 1 in 3 (29%) had no sign of cancer five years after their surgery. Although most patients (68%) who were able to have surgery had metastatic tumors confined to their livers, some had tumors in other parts of the body that were also removed during surgery. The lead investigator concluded as follows: “the folfoxiri regimen allows a complete resection surgery in approximately 1 out of 5 patients with initially unresectable metastatic colorectal cancer, and the long term survival of resected patients is considerable. Neoadjuvant folfoxiri for 3-6 months is safe and not associated with severe liver injury. “

Masi, Gianluca, et al., Long-Term Outcome of Initially Unresectable Metastatic Colorectal Cancer Patients Treated with 5Fluorouracil/Leucovorin, Oxaliplatin, and Irinotecan (folfoxiri) Followed by Radical Surgery of Metastases Annals of Surgery, Vol 239, Number 3, March 2009, pp 420-425.

9. Outcomes for Mother and Baby Not Affected by Colorectal Cancer During Pregnancy (Mar. 3/09)

Women who are diagnosed with colorectal cancer during pregnancy or shortly after giving birth have no difference in survival than women who weren't pregnant. Their babies, while at risk for preterm birth, have equally healthy outcomes and survival as other infants. Researchers matched women with colorectal cancer and their infants to two other groups: pregnant women without colorectal cancer and age-matched women with colorectal cancer who weren't pregnant. Women with colorectal cancer were about twice as likely to have cesarean sections and had three times the risk for infections. They went also into labor early three times as often as pregnant women without cancer. However, neonatal outcomes were similar.

Dahling, Mary, et al., Pregnancy Associated Colon and Rectal Cancer: Perinatal and Cancer Outcomes. Journal of Maternal-Fetal and Neonatal Medicine, Published online December 16, 2008.

10. Rectal Tumor Shrinkage After Presurgical Chemoradiation Predicts Survival (Mar. 4/09)

Locally advanced rectal cancer is frequently treated with Neoadjuvant (Presurgical) chemoradiotherapy (chemotherapy + radiation therapy) to reduce local recurrence and possibly improve survival. The tumor response to chemoradiotherapy varies and may influence the prognosis after surgery. The more tumors shrink during chemotherapy and radiation before rectal cancer surgery, the better the chance that patients will survive and be cancer-free five years later. This study assessed tumor regression (shrinkage) and its influence on survival in patients with rectal cancer treated with chemoradiotherapy followed by curative surgery. Doctors in Ireland developed a simple, three point, tumor regression grade or TRG, to measure the amount of change during chemoradiotherapy before surgery to remove rectal cancer. After 5 years, all patients with the best tumor regression grade – complete or near complete response to Chemoradiation – were alive and disease-free. In a series of 126 patients with locally advanced rectal cancer (T3/T4 or spread into nearby lymph nodes), five year disease-free survival after chemoradiotherapy followed by surgery was 72%. 7% of patients had cancer recur locally in or near the rectum. After pathologists examined the surgical specimen, a standard score was used to grade response to Chemoradiation: complete or near-complete response (TRG1), partial response (TRG2), or no response (TRG3). Patients with near or complete response (TRG1) had 100% disease free survival at 5 years. For those with partial (TRG2) response, 5 year disease free survival was 71%. No response (TRG3) led to a 66% disease free survival. 6 in 10 patients had some response to the presurgical chemoradiotherapy. The

lead investigator concluded that tumor regression grade measured on a 3 point system predicts outcome after chemoradiotherapy and surgery for locally advanced rectal cancer.

Beddy D, et al., A simplified tumor regression grade correlates with survival in locally advanced rectal carcinoma treated with Neoadjuvant chemoradiotherapy. Annals of Surgical Oncology, Vol 15, Number 12, December 2008. Published Online.

11. Alberta Approves Cancer Drug Avastin For Coverage (Mar. 6/09)

Alberta has joined other provinces in approving Avastin, a high priced cancer drug that has been costing some patients and their families thousands of dollars per month. Avastin (bevacizumab) will be added to Alberta's approved drug list as of April 1, but anyone who has been paying out of pocket for the drug up until then will not be reimbursed. Avastin has been approved for use in Canada since 2005 and is used as a first-line treatment for metastatic colorectal cancer. Alberta initially rejected Avastin from Medicare coverage. More than half the provinces have already approved coverage of Avastin, including Ontario, British Columbia, Saskatchewan, Quebec, Newfoundland, and Nova Scotia.

http://chealth.canoe.ca/channel_health_news_details.asp?channel_id=12&relation_id=1622&news_channel_id=12&news_id=27494

12. Role of Oxaliplatin in the Treatment of Colorectal Cancer (Mar. 9/09)

Oxaliplatin is a third-generation platinum agent that has shown a definite role in the management of colorectal cancer. Oxaliplatin in combination with 5FU and leucovorin in the folfox4 regimen represents a new standard of therapy in the adjuvant (post surgical) as well as for the treatment of metastatic disease. The combination of oxaliplatin with xeloda in the Xelox regimen has been demonstrated to be not inferior to folfox4 in metastatic patients and it is under evaluation, with or without avastin, in the post-surgical management of resected patients. Folfox4 and Xelox regimens represent a backbone on which to add new targeted drugs such as avastin and erbitux. This study evaluated the efficacy of combination of oxaliplatin with xeloda in the Xelox and Folfox4 regimen in metastatic colorectal cancer patients, with or without avastin, in the post-surgical management of resected patients. Folfox4 plus Erbitux was also evaluated. The results from the study were as follows: Combination of avastin with either folfox4 or Xelox significantly prolonged the progression free survival and overall survival versus folfox4 or Xelox combined with placebo in metastatic colorectal cancer patients, while folfox4 plus erbitux produced a significantly greater activity than folfox4 alone in metastatic colorectal cancer patients with Kras wild type status.

Comella, Pasquale, et al., Role of Oxaliplatin in the Treatment of Colorectal Cancer. Therapeutics and Clinical Risk Management. Vol 5: 229-238.

13. Biothera To Release Data on Imprime PGG at 2009 ASCO Meeting (Mar. 9./09)

Biothera will release data from the first arm of its metastatic colorectal cancer trial at the American Society of Clinical Oncology (ASCO) annual meeting May 29-June 2 in Orlando, Florida. The dose-escalating study is evaluating the safety and efficacy of Biothera's Imprime PGG in combination with the standard of care erbitux and irinotecan for second and third line metastatic colorectal cancer patients. Imprime PGG is a targeted immunotherapeutic drug that works synergistically with monoclonal antibodies, such as erbitux, through specific innate immune cell activation. It works by activating a large population of the body's immune cells (neutrophils) to kill cancer cells. Unlike other drugs that trigger a broad innate immune response, Imprime PGG selectively activates immune cells without inducing systemic pro-inflammatory cytokines (proteins which trigger inflammation), which reduces potential side effects. According to the company, PGG has the potential to improve patient response rates for existing monoclonal antibody therapies, such as erbitux, in approved indications.

www.pr-inside.com

14. Long-Duration Presurgical Chemo Linked with Higher Risk of Liver Toxicity for Patients with Colorectal Liver Mets (Mar.11/09)

Researchers from MD Anderson Cancer Center, presenting at the 62nd Annual Cancer Symposium, Society of Surgical Oncology, concluded that extended preoperative chemo increases the risk of liver toxicity (commonly referred to as "blue liver") after liver resection for colorectal liver mets and that disease response depends more on the type of chemo rather than

on the regimen's duration. The study sought to determine how the length of chemo before surgery affected disease response and liver function after surgery in patients with colorectal cancer that had spread to the liver. Researchers identified 219 patients who had been treated with folfox either with or without avastin between August 1999 and December 2007 before having liver surgery. Patients who received 8 cycles or fewer were classified as the short-duration chemo group (157 patients) and patients who were treated with 9 or more cycles of chemo were classified as the long duration group (62 patients). Researchers compared the 2 groups and it turned out that they had similar outcomes. Differences began to emerge, however, on the basis of whether the folfox regimen included avastin. For both short and long duration chemotherapy groups, patients who were treated with folfox and avastin experienced complete or major disease response statistically significant more often than patients treated with folfox alone. **Long duration group patients, however, had statistically significantly more liver injury and liver dysfunction than patients in the short duration group.** The authors concluded that based on their data, taking 9 or more cycles of chemo was the only independent factor that could predict liver insufficiency after surgery and the type of chemotherapy (folfox plus avastin) has more impact on pathologic response than does the duration of chemotherapy.

2009 Society of Surgical Oncology, 62nd Annual Cancer Symposium, Zorzi, Dara et al., Presentation Title: Extended Preoperative Chemotherapy Does Not Improve Pathologic Response and Increases Postoperative Liver Insufficiency After Hepatic Resection for Colorectal Liver Metastases. Abstract 62.

15. Post Surgical Therapy with Monoclonal Antibody Edrecolomab Plus FU-based Therapy Does Not Improve Overall Survival in Stage III Colon Cancer Patients (Mar. 12/09)

Edrecolomab (Panorex or ED) is a murine IgG2A monoclonal antibody that targets the human tumor-associated antigen epithelial cell adhesion molecule (17-1A) that is found on the surface of breast and colon adenocarcinoma. Edrecolomab has been approved in Europe (Germany) since 1995, but has not been approved by the FDA. In this study, patients with stage III colon cancer were randomly assigned to one of two treatments after curative surgery. Patients in the first group received five infusions of ED together with FU-based chemo; patients in the second group received FU-based chemo alone. The primary objective that was measured was overall survival after a follow-up of five years. The patients that were assigned to the first group who received ED plus FU-based therapy showed a 5 year survival rate of **69.6%** while patients receiving FU-based therapy had an overall survival rate of **68.2%**. Investigators concluded that adding Edrecolomab to FU-based therapy in patients with stage III colorectal cancer exhibited no benefit for there was no statistical significant effect on overall survival.

Fields, Anthony, et al., Adjuvant Therapy with the monoclonal antibody Edrecolomab plus fluorouracil-based therapy does not improve overall survival of patients with stage III colon cancer. Journal of Clinical Oncology. JCO Early Release, published online ahead of print Mar 9 2009. 10.1200/JCO.2008.18.5710.

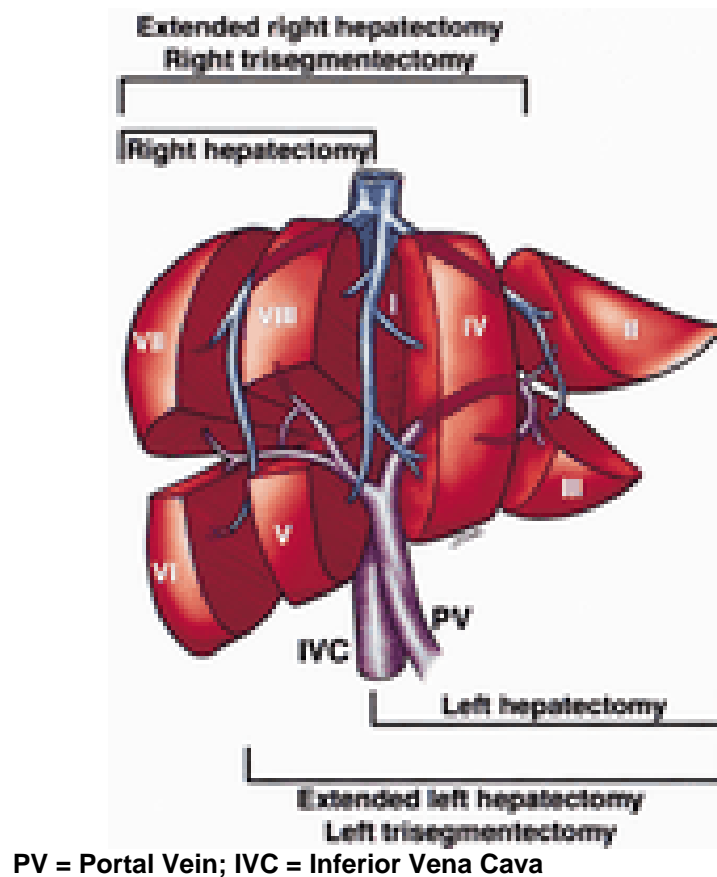
RADIATION/INTERVENTIONAL RADIOLOGY

16. Effect of Portal Vein Embolization on the Growth Rate of Colorectal Liver Mets (Feb. 10/09)

Portal vein embolization is a treatment used to cause the atrophy or shrinking of a part of the liver and the hypertrophy or extra growth of the remaining liver. The setting in which this can be of benefit is in the preoperative patient in which you need to shrink the bad liver that you are going to remove and grow the good liver that you are going to leave behind. This is a useful technique in some patients in which a large resection needs to be done and the remaining liver will be a fairly small volume. Portal vein embolization involves the insertion of a catheter into the portal vein through the liver. Contrast material ("dye") is injected to define the anatomy of the portal venous system. Selective branches of the portal vein are then blocked with small particles and metal coils until the flow of blood is stopped. Growth of the non-embolized portion of the liver usually takes 3-4 weeks and CT is used to document the change. A 1-2 day hospital stay is typical following the procedure.

According to this study, investigators note that for colorectal cancer metastases to the liver, portal vein embolization (PVE) is used to increase the remnant liver before major liver resection. The resection rate after PVE is 60-70%, mainly limited by disease progression. The effect of PVE on tumour growth rate has not been investigated very much clinically. The objective of this study was to compare the growth characteristics of resected colorectal liver mets in patients undergoing pre-operative PVE with those of match controls who had not undergone PVE. There were 22 patients who had undergone preoperative PVE and 20 matched controls. Tumor growth rate was measured by the change in tumour volume using CT and MRIs from diagnosis to resection. The rate at which tumours grew was more rapid in the PVE group compared with

that in controls. Investigators concluded that tumour growth rate increased following PVE and that this is related to increased tumour cell division.



Source: <http://radiographics.rsnajls.org/cgi/content/full/22/5/1063>

Pamecha, V et al., Effect of portal vein embolization on the growth rate of colorectal liver metastases. *British Journal of Cancer*. 2009; 100, 617-622.

17. Response to Radiation Treatment before Surgery Improves Rectal Cancer Survival (Feb. 17/09)

Patients whose tumors shrink in response to radiation therapy before surgery for rectal cancer have both improved overall survival and improved disease-free survival. However, even patients who responded to presurgical radiation did not reach survival rates equal to those patients with stage I disease undergoing resection alone. Researchers studied nearly 11,000 rectal cancer patients – 3700 who were treated with neoadjuvant (presurgical) radiotherapy and 7200 who had stage I cancer and received only surgery as a form of therapy. The results were as follows:

- For patients who responded to presurgical radiotherapy, 94% were alive cancer free 5 years later compared to 78% of those who didn't respond with tumour shrinkage
- Overall survival at 5 years was 82% in responders, 60% in those with no tumour downstaging (downstaging = the conversion of an unresectable tumor to resectable)
- For stage I patients with surgery only, disease-free survival at 5 years was 97%, overall survival was 79%

Investigators concluded the following: Patients with rectal cancer downstaged after neoadjuvant radiotherapy have improved survival compared with nonresponders. While disease-free survival is excellent for responders to neoadjuvant radiotherapy, it did not equal the disease-free survival of patients with stage I disease undergoing resection alone.

Castaldo, Eric. et al., Improvement of survival with response to neoadjuvant radiation therapy for rectal cancer. *Archives of Surgery*: 2009; 144(2): 129-134.

18. Relapse Rate is Halved in Rectal Cancer (Mar. 9/09)

Rectal cancer patients who receive a combination of improved surgical techniques and short-course radiotherapy before surgery have a strong chance of remaining cancer-free, according to 2 articles published in the *Lancet*. The studies show that high quality surgery and a five day course of radiotherapy cuts recurrence rates to just 1% compared with about 13% with standard surgery alone. One report assessed how the amount of tissue removed around the tumour by surgeons affected the rates of rectal cancer recurrence. The findings, based on 1156 patients from the UK, Canada, South Africa and New Zealand, with operable rectal cancer, shows that surgery rated as "good" that removes the whole of the rectum – known as the **mesorectal plane**

– is the most successful. This high quality surgery technique is already being used by surgeons. At present, only **50%** of rectal cancer surgery is done in the **mesorectal plane**, suggesting that a further decrease in local recurrence rates might be obtained by improving the plane of surgery. The second study compared the effectiveness of short course pre-operative radiotherapy, with a 5 week course of radiotherapy and chemotherapy reserved for those patients considered at high risk of the cancer returning. The reason for the latter option was that radiation given in the pelvic area can lead to sexual and bowel problems. 1350 patients were randomly assigned either 5 daily treatments of radiotherapy followed by surgery, or surgery followed by 25 treatments of radiotherapy and chemotherapy for those at high risk of a local recurrence. Findings show that after 3 years **4% of patients in the radiotherapy group had a local recurrence**, compared with **11% of patients in the surgery and selective treatment group**. Lead investigator concluded that these studies add further weight to the argument that the quality of surgery achieved improves outcomes in rectal cancer patients and that short course pre-operative radiotherapy improves them even more, even when good surgery has been performed.

Sebag-Montefiore, David, et al., Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomized clinical trial. The Lancet, Vol 373, Issue 9666, pp 821-828

Sebag-Montefiore, David, et al., Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTC CO16): a multicentre, randomized trial. The Lancet: Vol 373; Issue 9666, pp 811-820.

SCREENING

19. Colorectal Cancer Screening Reduces Mortality (Feb. 23/09)

March is colorectal cancer awareness month and the implementation of colorectal cancer screening appears to reduce mortality from the disease, as evidenced by the disparity between mortality rates among regions that implemented screening at different times. Because colorectal cancer is a type of cancer that is highly curable in early stages, universal screening of individuals remains of utmost importance in order to improve overall outcomes for the disease. In the US and Europe, colorectal cancer incidence and mortality are on the decline, which is possibly related to the implementation of regular screening. One common screening procedure is the fecal occult-blood test (FOBT), which checks for hidden blood in the stool. In an effort to evaluate the efficacy of colorectal cancer screening, researchers in Italy compared the colorectal cancer mortality rates of two geographic areas in the provinces of Florence and Prato in the Tuscany region of Italy that implemented screening programs at different times. The Empolese-Mugello district began screening with FOBT in the early 1980's, whereas the rest of the Florence and Prato provinces began in early 2000. In the Empolese-Mugello district, approximately 175,000 people were tested each year with FOBT compared with approximately 38,000 in the rest of the Florence and Prato provinces (beginning about 15 years later). The results indicated that the Empolese-Mugello district had a greater decrease in colorectal cancer mortality than the rest of the Florence and Prato provinces. The estimated annual reduction in age-adjusted colorectal cancer mortality was 2.7% in the Empolese-Mugello district compared with 1.3% in the rest of the Florence and Prato provinces. **The researchers concluded that the “observed difference in colorectal cancer mortality is due to earlier exposure to fecal occult blood test screening.”**

Costantini AS, et al., Colorectal cancer mortality in two areas of Tuscany with different screening exposures. J of the National Cancer Institute. 2008: 100: 1818-1821

SURGICAL

20. The Risk of Cancer After Polyp Removal (Mar. 11/09)

There are very few studies that have examined the risk of developing advanced adenomas and cancer after the removal of polyps through colonoscopy (polypectomy) or the factors that determine risk. Researchers pooled 8 studies that followed up 9167 men and women aged 22 to 80 with previously removed polyps during a colonoscopy. Researchers found 1082 with a later advanced adenoma and 58 with colorectal cancer. The average follow up time was 47 months. Risk for advanced adenomas or cancer were greatest for those who had 5 or more polyps removed originally. One in four (24.1%) would have either a large polyp or cancer within 5 years. One in five (19.3%) would have advanced lesions when the original polyp was more than 2 cm. Men appeared to be at higher risk as were older patients. Risk was also increased when the original polyp was found in the right side of the colon, and when it had villous features. (Appearing to have microscopic finger-like projections – villi - that line the inner wall of the small intestine.) The lead investigator concluded that the occurrence of advanced colorectal neoplasia

is common after polypectomy. Factors that are associated most strongly with risk of advanced neoplasia are patient age and the number and size of prior adenomas.

Martinez, Elena et al., A Pooled Analysis of advanced Colorectal Neoplasia Diagnoses After Colonoscopic Polypectomy. Gastroenterology. Vol 136, Issue 3: pp 832-841. March 2009.

OTHER

21. NCCN Adds Survivorship Section to Colon and Rectal Cancer Guidelines (Feb. 18/09)

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 21 of the world's leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer. They create clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision makers. A significant addition to the NCCN Guidelines is a new section dedicated to survivorship that provides recommendations for long-term follow up care of patients treated for colorectal cancer. Specific information is provided about managing possible long term side effects of treatment, routine screening and monitoring, healthy lifestyle and wellness counseling and making the transition back into the care of a primary care physician. Other important additions include new indications for erbitux as it relates to Kras gene testing and recommendations on how to re-evaluate patients initially presenting with unresectable disease. Those wishing to visit NCCN's practice guidelines may do so at www.nccn.org.

www.nccn.org/about/news/newsinfo-asp?NewsID=202

22. Colorectal Cancer Patients who are Informed Access Newest Drugs (Feb. 23/09)

Cancer patients who research treatment options are 3 times more likely to access the newest drugs than patients who don't spend extra time learning about their condition, according to a study of 633 patients with colorectal tumors. Patients who sought information from the Internet, newspapers, and magazines were more likely than others to have heard of the "targeted" therapies erbitux and avastin. But those who pursued second opinions from doctors as part of their research were the most likely actually to be prescribed these drugs, according to Dana Farber Cancer Institute in Boston. The FDA approved Erbitux and Avastin in 2004 because they slow tumor growth, though they do not cure cancer. They are approved for metastatic disease. But one in four people who received the drugs accessed them "off label" for early disease, an unapproved use. The authors note that off-label drug use is common in cancer. Patients who try new cancer drugs may benefit, the authors say, but also may suffer from side effects. Avastin increases the risk of strokes, heart attacks, and serious blood clots. Erbitux can cause a disfiguring rash. Nevertheless, the researchers found that high levels of information seeking were strongly associated with both awareness of and receiving treatment using targeted therapies. Patients who sought information about treatments for colorectal cancer were 2.83 times more likely to have heard about targeted therapies and 3.22 times more likely to have received targeted therapies than people who did not seek information.

Gray, Stacey, et al., Colon cancer patient information seeking and the adoption of targeted therapy for on-label and off-label indications. Cancer. April 1, 2009. Published Online (DOI: 10.1002/cncr.24186)

23. Test May Help Predict Recurrence Risk in Early Colorectal Cancer (Feb. 24/09)

Testing lymph nodes for the presence of a protein known as guanylyl cyclase 2C (GUCY2C) may help predict risk of recurrence among colorectal cancer patients with no apparent lymph node mets. When colorectal cancer is detected early – before it spreads to nearby lymph nodes or other parts of the body – survival rates are high and treatment often consists of surgery alone. Nevertheless, an estimated 25% of patients with early, apparently node-negative colorectal cancer will develop a cancer recurrence following treatment. Some of these patients may have had undetectable lymph node mets at the time of their initial diagnosis. Newer approaches to testing lymph nodes may better identify patients with early signs of lymph node mets and a higher risk of recurrence. These patients may benefit from more aggressive approaches to treatment. GUCY2C is a protein that is expressed by crc. Researchers hypothesized that the presence of this protein in lymph nodes – where it is not usually found – could indicate that the cancer has spread to the lymph nodes, and that the patient is at increased risk of recurrence. In this study, 257 colorectal cancer patients who had no evidence of lymph node involvement were tested for GUCY2C in their lymph nodes and patients were then followed for 2 years.

- 87.5% of patients had lymph nodes that tested positive for GUCY2C

- The risk of recurrence was 21% among patients with lymph nodes that tested positive for GUCY2C, but only 6.3% among patients with lymph nodes that tested negative for GUCY2C

The results suggest that testing lymph nodes for GUCY2C provides information about recurrence risk among patients with early colorectal cancer, which could help guide treatment decisions.

Waldman, SA, et al., Association of GUCY2C expression in lymph nodes with time to recurrence and disease free survival in pNO colorectal cancer. J of the American Medical Association. 2009: 301: 745-752

24. **Colorectal Cancer Patients in Poor Condition Can Still Benefit From Chemotherapy** (Mar. 5/09)

Advanced colorectal cancer patients with poor performance status still derive benefit from chemotherapy, although with a higher risk of toxicity and death, according to this study published in the Journal of Clinical Oncology. Mayo Clinic researchers retrospectively compared treatment efficacy in 6286 clinical trial patients with metastatic colorectal cancer, where 509 patients had a poor performance status (performance status of **2**). They note that patients with a poor performance status often comprise less than 10% of patients in clinical trials. Researchers found that patients with a poor performance status benefited just as much from modern chemotherapy regimens as patients with a better performance status (performance status of **0 or 1**) in terms of progression free survival, overall survival and response rate; although all three remained significantly lower for patients with poor performance status. However, treatment was associated with significantly more toxicity, including nausea of grade 3 or higher and vomiting etc. Lead investigator concluded that on the basis of their results, **oncologists can feel confident that treating patients who present with poor performance status as a result of their cancer with maximally effective chemotherapy is likely to provide patient benefit, however, regardless of regimen, these patients need to be managed attentively with supportive care.**

Sargent, Daniel, et al., Pooled Safety and efficacy analysis examining the effect of performance status on outcomes in nine first line treatment trials using individual data from patients with metastatic colorectal cancer. Journal Clinical Oncology. Published online ahead of print. March 2, 2009. 10.1200/JCO.2008.20.2879

25. **Distress Linked to Lower Physical Activity in Colorectal Cancer Patients** (Mar.6/09)

Colorectal cancer patients, who show high levels of somatization, or physical symptoms of psychological distress, are less likely to be physically active, while patients who have a more positive view of their cancer are more likely to be physically active, according to the results of this study. Researchers surveyed 978 colorectal cancer survivors and found that patients with higher levels of distress/anxiety had higher levels of physical inactivity. In contrast, patients who had a more positive appraisal of their cancer were less likely to be inactive or insufficiently active. Lead investigator concluded that the lack of a clear relationship between higher psychological distress and increasing physical activity argues against distress as a motivator to exercise in these patients.

Chambers, Suzanne, et al., Relationship Over Time Between Psychological Distress and Physical Activity in Colorectal Cancer Survivors. Journal of Clinical Oncology. Published online ahead of print. March 2, 2009. 10.1200/JCO.2008.18.5157

26. **Study Indicates Age Differences in Rectal Cancer Treatment** (Mar. 11/09)

New research from Sweden indicates that rectal cancer patients 75 and older are less likely to undergo radiation before undergoing surgery than are younger people with the disease. The analysis of data from about 15,000 patients treated for the disease between 1995 and 2004 also showed that older patients were less likely to have advanced disease, but also less likely to survive for 5 years after diagnosis. To investigate whether there might be age-related differences in rectal cancer treatment, researchers analyzed data from the Swedish Rectal Cancer Registry, which includes nearly all patients diagnosed with the disease in Sweden since 1995. They looked at 15,104 patients, of whom 42.4% were 75 or older. About 15% of the older patients had disease that had spread beyond the colon, compared to nearly 18% of the younger patients, the researchers found. The older patients were less likely to have had abdominal surgery to remove their tumors; 68.5% had this procedure, compared to 84.4% of younger patients. The researchers also found that the older patients were more than three times as likely as the younger patients to have had an operation called Hartmann's procedure, which requires a colostomy. And while 67.2% of the younger patients had radiation treatment before surgery, just 34.3% of older patients did. In terms of survival, 73% of the older patients treated with intent to cure lived for 5 years or longer, while 78% of the younger patients did. Tumors recurred in the rectal area for 9% of the older patients and 8% of the younger patients.

NUTRITION

27. People Who Exercise Lower Their Risk of Colon Cancer (Feb. 11/09)

A new study has added considerable weight to the claim that exercise can lower the risk of colon cancer. Researchers at Washington University School of Medicine and Harvard University combined and analyzed several decades worth of data from past studies on how exercise affects colon cancer risk. They found that people who exercised the most were 24% less likely to develop the disease than those who exercised the least. What is most compelling is the association between exercise and lower colon cancer risk regardless of how physical activity was measured in the studies. The lead investigator comments that this is a robust association and gives all the more evidence that physical activity is truly protective against colon cancer. The study suggests that if the American population became significantly more physically active, up to 24%, or more than 24,000, fewer cases of colon cancer would occur each year. The study found that the protective effect of exercise held for all types of physical activity, whether that activity was recreational, such as jogging, biking or swimming or job related, such as walking, lifting or digging. And the beneficial effect of exercise held for both men and women. This study highlighted the fact that there is an ever-growing body of evidence that the behaviour choices we make affect our cancer risk. Physical activity is at the top of the list of ways that you can reduce your risk of colon cancer.

Wolin KY, et al., *Physical Activity and colon cancer prevention: a meta-analysis. British Journal of Cancer. Feb.10, 2009. 611-616. (Advance Online Publication) doi:10.1038/sj.bjc.6604917.*

28. No Benefit for Multivitamins in Preventing Women's Colorectal Cancer (Feb. 12/09)

Regular use of multivitamins didn't reduce risk for colorectal and other cancers in a diverse group of 162,000 women from sites across the United States. After eight years of follow-up, there was no significant difference in cancer, heart disease, or death between multivitamin users and those who didn't take the supplements. About 40% of women in the Women's Health Initiative took multivitamins on a regular basis. In the almost 9600 cases of breast, colorectal, endometrial, stomach, lung and ovarian cancer, there were no differences between postmenopausal women who used multivitamins and those who didn't.

www.C3:ColorectalCancerCoalition.com/Research&TreatmentNews

Rebuttal to the above-noted study: <http://elistman.stopagingnow.com/view.php?>

29. Vitamin B3 Fuels Neutrophil Production (Feb. 23/09)

As the first line of defense against invading microbes, neutrophils are the "foot soldiers" of the innate immune system. Made and released from the bone marrow, neutrophils circulate in the blood for only a few hours before housing themselves in body tissues where they survive at most for 2 or 3 days. To keep up with the heavy demand for these short-lived cells, a normal healthy adult produces approximately 1011 neutrophils each day and up to 10 times that number in the setting of an infection. Cancer patients undergoing chemo often experience disruptions in neutrophil production, which places them at increased risk for infection. Neutrophil production has been boosted with the use of recombinant granulocyte colony stimulating factors (G-CSF – ie. neupogen and neulasta). But the mechanism in which it does so remains poorly understood. A team of researchers from Germany recently reported a major breakthrough in neutrophil development that may have important clinical implications. G-CSF turns on an enzyme that converts intracellular vitamin B3 (nicotinamide) into an active metabolite (nicotinamide mononucleotide). Addition of vitamin B3 or its precursor induced granulocyte differentiation of cultured hematopoietic stem cells. Adding high doses of vitamin B3 to 6 healthy individuals resulted in significant increases in neutrophil count over a 7 day period and a return to normal cell counts when vitamin B3 was withdrawn. These results identify a new role for vitamin B3 in granulopoiesis and beg for clinical trials to evaluate the use of vitamin B3 either alone or in combination with G-CSF for the treatment of neutropenia (low neutrophil counts).

Skokowa J, et al., *NAMPT is essential for the G-CSF-induced myeloid differentiation via a NAD⁺-sirtulin-1-dependent pathway. Nat Med. 2009; 15 (2): 151-158.*

30. **A Diet That is Rich in Calcium May Reduce risk of Colorectal Cancer** (Feb. 23/09)

A diet that is high in calcium whether through food or supplements may be associated with a reduced risk of cancer, especially colorectal cancer, according to the results of a study published in the Archives of Internal Medicine. The NIH-AARP Diet and Health Study was designed to evaluate dairy food and calcium intakes in relation to cancer. Study participants responded to a food frequency questionnaire that allowed researchers to determine their intake of dairy food as well as calcium from other foods and supplements. Over a seven year period, the researchers identified 36,965 men and 16,605 women with cancer. There was no relationship between calcium intake and overall cancer incidence in men. In women, the risk of cancer decreased with increasing calcium intake up to approximately 1300 mg/day; however, further increases in calcium intake did not decrease cancer incidence. In men and women, increased calcium intake was associated with a decreased incidence of cancer of the digestive tract. Men with the highest intake of calcium had a 16% reduction in the incidence of digestive tract cancers compared with men with the lowest calcium intake. Women with the highest intake of calcium had a 23% reduction in the incidence of digestive tract cancers compared with women with the lowest calcium intake. The effect of high calcium intake was the greatest in the prevention of colorectal cancers in both men and women, leading the researchers to conclude that "calcium intake is associated with a lower risk of total cancer and cancers of the digestive system, especially colorectal cancer."

Park Y, et al., Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. Archives of Internal Medicine. 2009; 169: 391-401

31. **Fruit & Vegetable Intake Are Associated With Lower Risk of Colorectal Adenomas** (Feb. 23/09)

Many phytochemicals (substances, such as a flavonoid or carotenoid, found in plants considered to have a beneficial effect on human health). in fruits and vegetables have been shown to have cancer-inhibitory effects in animal studies. These effects on cancer, however, have not been clearly shown in human studies. This study investigated the association between fruit and vegetable intakes and the risk of developing adenomas. Participants were aged 40–75 years and were recruited from patients undergoing colonoscopy at 2 medical centers in Nashville, Tennessee from 2003 to 2005. Cases had at least one adenoma and controls were polyp free. Results revealed that increased intakes of total fruits, berries, fruit juice, and green leafy vegetables were associated with reduced adenoma risk. This study provides additional evidence that high total fruit intake and certain fruit and vegetable intakes may be associated with a reduced risk of colorectal adenomas.

Wu, H et al., Fruit and Vegetable intakes are associated with lower risk of colorectal adenomas. Journal of Nutrition. 2009 February; 139(2): 340-344.

32. **High Fat Diet Fuels Cancer Spread** (Feb. 28/09)

Past studies have shown that obesity may contribute to cancer. Purdue University researchers have now shown that eating a high fat diet fuels the spread of cancer, by feeding cancer cells, promoting metastasis. Fat in lipids seems to provide energy to cancer cells, making them mobile. By using special imaging techniques, Purdue researchers were able to watch the process of how cancer cells disengage from each other, travel in the blood stream, and spread to other parts of the body when a high fat diet was given to mice in the laboratory. If the cancer cells don't have excess lipids, they stick together and form very tight junctions in tumors, but increasing lipids causes them to take on a rounded shape and separate from each other. The findings showed a 300% increase in the spread of cancer when mice in the study were given a high fat diet. The researchers found that polyunsaturated fats allowed cancer cells to change shape and enter the blood stream. The scientists used a technique called intravital flow cytometry to count cancer cells in the bloodstream of the mice fed a high fat diet, comparing to those fed a low fat diet. They documented changes that occurred in the cancer cells after the mice ate a high fat diet. According to Ji-Xin Cheng, an assistant professor in Purdue's Weldon School of Biomedical Engineering and Department of Chemistry, "It is generally accepted that diet and obesity are accountable for 30% of preventable causes of cancer, but nobody really knows why. These findings demonstrate that an increase in lipids leads directly to a rise in cancer metastasis." The change in shape of cancer cells, brought about by a high fat diet, seems to be essential for fueling the spread of cancer. The researchers plan more studies to find out exactly what role obesity plays in causing cancer and how fat and high fat diets fuel the spread of cancer.

<http://www.emaxhealth.com/1020/1/29492/high-fat-diet-fuels-cancer-spread.html>

33. Magnesium Deficiency Linked to Colorectal Cancer (Feb. 25/09)

A Swedish study found that women who had the lowest magnesium intake had the highest rates of colorectal cancer compared to women who had high magnesium intake. The study results also suggest that magnesium may help prevent colorectal cancer in women. Study participants were 61,433 of Swedish women, ages 40 to 75, living in a region of central Sweden. Data gathering used mail-in questionnaire in compiling women's dietary habits, weight, height and education. These women were enrolled in the study between 1987 and 1990. With a mean follow-up of 14.8 years, findings showed 805 women were diagnosed with colorectal cancer; 547 with colon cancer, and six with both colon and rectal cancer. Investigators found women who had high magnesium intake generally consume more dietary fiber, zinc, beta-carotene, folate and vitamin B6, and ate less saturated fat.

http://blog.worldvillage.com/health/magnesium_deficiency_linked_to_colorectal_cancer.html

34. Black Raspberries Reduce Colorectal Inflammation and Polyps (Mar. 9/09)

Freeze-dried berries reduced the inflammation that contributes to colorectal cancer in both humans and mice, the number of tumors in mice, and new rectal polyps in patients with familial adenomatous polyposis. After treatment with berries, levels of proteins that control inflammation were reduced in patients with colorectal cancer.

In the first study, patients with ulcerative colitis are at increased risk to develop colorectal cancer, probably because of excessive inflammation in their intestinal tracts. Scientists at Northwestern University in Chicago and Ohio State University in Columbus experimented with mice that were bred missing an important anti-inflammatory signaling molecule (*cytokine*) interleukin-10. All the mice developed an inflammation of their colons (*colitis*).

Beginning when the mice were four weeks old, the researchers added 5% or 10% concentrations of freeze-dried black raspberry powder to the animals' diets. After 23 weeks,

- 10 out of 14 mice (71%) that had a normal diet with no berry supplements developed colorectal cancer tumors.
- 5 out of 13 (38%) that had 5% concentration of berry powder in their food developed tumors.
- 4 out of 13 (31.8%) that were fed the 10% concentration developed tumors.

In addition, the black raspberry powder significantly reduced colon inflammation, ulcers, and changes in the colon lining of the mice. The team concluded that black raspberries had the potential to prevent inflammation-related development of colon cancer.

The second study revolved around patients with an inherited colon cancer called *familial adenomatous polyposis* (FAP) who develop hundreds, sometimes thousands, of polyps in their colons and rectums. Without intervention, all FAP patients will develop colorectal cancer, usually by the age of 40. Standard treatment for FAP is surgical removal of the colon with regular surveillance of the rectum and removal of rectal polyps. Fourteen FAP patients whose colons had been removed were treated with black raspberries. Seven drank black raspberry powder in water every day for nine months. They also used two black raspberry suppositories in their rectums at bedtime. Another seven drank a placebo, but inserted the suppositories. Rectal polyps were counted at the beginning of treatment and nine months later. The entire group had a median 43% reduction in polyp count. Those who used both the drink and the suppositories had greater reductions in polyps of 59%, compared to 36% in those who had a placebo drink. Tissue was collected from both polyps and the crypts lining the colon that is being analyzed to find out what molecular mechanisms are at the bottom of the reductions.

Liao, Jie et al., Abstract PR-13: Inhibition of chronic colitis-induced carcinogenesis in IL-10 knockout mice by dietary supplementation of black raspberries. Cancer Prevention Research. I (7 Supplement) PR-13; doi: 10.1158/1940-6207.PREV-08-PR-13

Stoner, Gary, et al., Abstract PR-14: Regression of rectal polyps in familial adenomatous polyposis patients with freeze-dried black raspberries. Cancer Prevention Research. I (7 Supplement) PR-14, November 1, 2008. doi: 10.1158/1940-6207.PREV-08-PR-14