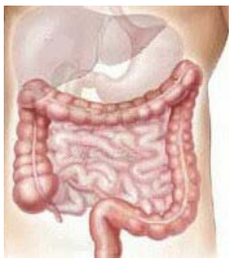
COLORECTAL CANCER RESEARCH

Month Ending October 16, 2009



The following colorectal cancer research update extends from September 19 – October 16, 2009 inclusive and is intended for informational purposes only.

CONTENT

NUTRITION / HEALTHY LIFESTYLE

DRUGS / SYSTEMIC THERAPIES

1. New Colorectal Cancer Antibody Beginning Phase I Trial in Late Stage Colorectal Cancer (Sept. 18/09)

NPC-1C, developed by Neogenix Oncology, is entering a Phase I trial. NPC-1C is derived from a colorectal cancer vaccine that had previously demonstrated safety and clinical activity in prior human studies. It is a novel, monoclonal antibody intended for the treatment of **advanced** pancreatic and **colorectal cancer**. This first human trial will evaluate the safety of NPC-1C in patients with **late-stage** pancreatic or colorectal cancer and will be evaluated in 12-24 patients which should provide important additional data regarding the safety and activity of the antibody. The trial is expected to complete enrollment in approximately 6-8 months.

http://www.drugdeliverytech.com/ME2/dirmod.asp?sid=&nm=&type=news&mod=News&mid=9A02E3B96F2A415ABC72CB5F516B4C10&tier=3&nid=09B7438524EF4F22B9FB5A69BA677D68

2. Aspirin To Prevent Colon Cancer in Lynch Syndrome (Sept. 21/09)

This study has discovered that taking two aspirins a day can help people who are genetically susceptible to colon cancer. Researchers believe that this study may have found a simple way of controlling stem cells that make tumors grow. They believe that aspirin may have an effect on the survival of aberrant (faulty) stem cells in the colon. The European researchers tracked more than 1,000 people with Lynch syndrome, a genetic mutation that makes them vulnerable to cancers in the colon, rectum, stomach, brain, liver, uterus and elsewhere. The syndrome accounts for about 5% of all colon cancers. Half of the people in the study were given 600 milligrams or two aspirin daily, while the other half got placebo pills for about four years. In the group that received aspirin, six people developed colon cancer, versus 16 in the group that got placebos. Even though they stopped giving the aspirin after four years, the effect of the aspirin is apparently continuing. This discovery may mean aspirin could help prevent colon cancer. This doesn't mean that everyone should start taking aspirin if they're worried about bowel cancer, for aspirin can cause signficant side effects if not used as directed by a physician. Based on this research, where patients did not benefit until several years after taking aspirin, researchers believe the drug may also affect cancer stem cells. They hypothesized aspirin might speed up the process by which cells destroy themselves if they pick up "genetic spelling mistakes" that could be cancerous. That could result in a protective effect against cancer ever developing. Other scientists were not convinced that stem cells were involved. Researchers plan to study whether a lower dose of aspirin will also ward off colon cancer. What is important is studies are beginning to show that aspirin could help prevent colon cancer.

Burn, J., et al., Aspirin Prevents Cancer in Lynch Syndrome. European J of Cancer Supplements, Vol. 7, No. 3, September 2009, page 320.

3. Roche Presented New Survival Data From Phase II and III Trials (Sept. 21/09)

Significant advances in the early treatment of colon cancer using Xeloda (capecitabine) in combination with standard chemotherapies as well as strong phase II, III, and IV data for avastin confirming the benefits of targeting VEGF inhibition to control cancer growth in advanced colorectal cancer was presented in Berlin on September 21. The phase III trial was the first efficacy results from the “Xeloxa” adjuvant study, the largest trial completed in patients with stage III colon cancer, showing significant disease-free survival benefits with oral Xeloda in combination with intravenous oxaliplatin (Xelox) vs. 5FU immediately following surgery. In the phase II trial, results from BOXER showed the percentage of patients with liver-only mets from their colorectal cancer and unsuitable for upfront liver surgery who became eligible for potentially life-saving (curative) surgery when treated with avastin plus xeloda and oxaliplatin. The study also showed the rate of shrinkage or disappearance of treated liver mets.

Haller, D et al., 5LBA First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5FU/LV for stage III colon cancer (NO16968/Xeloxa study). European J of Cancer. Vol. 7, Issue 3, page4 (Sept. 2009)

4. Determining The Efficacy of Avastin (Sept. 21/09)

A couple months ago, the FDA approved Avastin for use in treating brain cancer as well as there being prior approvals for the treatment of lung, breast, colorectal and other cancers. However, the effectiveness of avastin is highly variable on a case-by-case basis. While some patients experience a considerable increase in survival time thanks to the drug, Avastin only delivers a 2-month increase in expected overall survival when compared to other drug treatments. Initially heralded as a breakthrough drug, doctors are now coming to realize a vast set of complexities behind the effectiveness of Avastin. Avastin works by blocking a cancer's ability to feed a growing tumor with new blood vessels. This is accomplished by inhibiting the function of a vascular endothelial growth factor (VEGF) protein that is responsible for stimulating formation of new blood vessels. When successful, Avastin deprives a tumor of oxygen, limiting or reversing growth. However, for too many patients, the drug has no effect at all. The variability of success is based on genetic variations present in a patient. Unfortunately, the responsible DNA has yet to be identified which would be a predictor of efficacy. In absence of more targeted answers, doctors continue to prescribe Avastin to a high number of cancer patients in the hopes that they will respond positively. However, a relatively low number of patients are favorably affected by the treatment. Researchers at Genentech (Avastin's manufacturer) have already sifted through 150 genetic markers in the hopes of identifying pertinent genes responsible for avastin's efficacy or lack thereof. Hopefully, these considerable efforts will lead to genetic discoveries that doctors can use to predict the effectiveness of Avastin in future patients.

www.technologyreview.com/biomedic

5. Adding Avastin (Bevacizumab) to Xeloda (Capecitabine) Improves Progression Free Survival in mCRC (Sept. 22/09)

Adding bevacizumab (avastin) to capecitabine (Xeloda), **without or with mitomycin C**, significantly improves progression-free survival (PFS) compared with capecitabine alone in the first-line treatment of previously untreated patients with metastatic colorectal cancer (mCRC). These final results were presented at the joint 15th Congress of the European Cancer Organization (ECCO) and 34th Congress of the European Society for Medical Oncology (ESMO). The median survival for patients with metastatic colorectal cancer has increased over the last 20 years, however, prognosis still remains poor, and not all patients are fit for the standard combination chemotherapy. The study included patients with unresectable mCRC with no prior chemotherapy other than adjuvant therapy (post surgical therapy), and no relapses for the prior 6 months. Patients were randomized according to age (>= 65 years vs. < 65 years) and capecitabine dose. The overall response rate was 30% for patients receiving capecitabine alone, 38% for patients receiving capecitabine plus bevacizumab, and 46% for patients receiving triple therapy consisting of capecitabine, avastin and mitomycin. All treatments were well tolerated. There were no significant differences in any of the toxicities observed, except for hand and foot syndrome. There were also no differences seen for quality-of-life assessments and for median overall survival Researchers concluded that capecitabine and bevacizumab is an active, low-toxicity regimen that may be considered as a possible option for patients with metastatic colorectal cancer.

Tebbutt, NC, et al., International randomized phase III study of capecitabine, bevacizumab, and mitomycin C in first line metastatic colorectal cancer: Final results of the AGITG MAX trial. J of Clinical Oncology. Vol. 27, No. 155; 2009: 4023

6. Vectibix (Panitumumab) + Folfiri Delays Progression of mCRC (Sept. 23/09)

Among patients with previously treated, metastatic colorectal cancer, the addition of the targeted therapy Vectibix (panitumumab) to folfiri chemotherapy delayed cancer progression. This benefit was only observed in patients whose tumors did not contain a mutation in the KRAS gene. These results were presented at a major European cancer conference. Targeted therapies are anticancer drugs that interfere with specific pathways involved in cancer cell growth or survival. Some targeted therapies block growth signals from reaching cancer cells; others reduce the blood supply to cancer cells; and still others stimulate the immune system to recognize and attack the cancer cell. Depending on the specific "target," targeted therapies may slow cancer cell growth or increase cancer cell death. Vectibix inhibits cancer cell growth and survival by targeting a protein known as the epidermal growth factor receptor (EGFR). Vectibix appears to benefit only those patients whose cancers do not contain a mutation in a gene known as KRAS. KRAS mutations occur in an estimated 40-50% of metastatic colorectal cancers and can be identified by testing a sample of tumor tissue. To evaluate the effectiveness of Vectibix in the **second-line treatment** of metastatic colorectal cancer, researchers conducted a Phase III clinical trial among 1,186 patients. Study participants were assigned to receive treatment with FOLFIRI chemotherapy alone or FOLFIRI plus Vectibix.

- Among patients without KRAS mutations (known as wild type), the addition of Vectibix improved progression-free survival. Progression-free survival was 5.9 months among patients treated with chemotherapy plus Vectibix compared with 3.9 months among patients treated with chemotherapy alone. The addition of Vectibix did not significantly improve overall survival.
- Among patients with KRAS mutations, the addition of Vectibix did not improve progression-free or overall survival.

- Side effects of Vectibix included skin rash, low magnesium levels, and diarrhea.

The results of this study suggest that the addition of the targeted therapy Vectibix to second-line chemotherapy improves progression-free survival among patients with metastatic colorectal cancer. The benefit only applies to patients whose tumors do not contain KRAS mutations

Peeters M, et al. Randomized phase 3 study of panitumumab with FOLFIRI vs FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC). Presented at the Joint ECCO 15-34th ESMO Multidisciplinary Congress. Berlin, Germany, September 20-24, 2009. Abstract 14LBA.

7. Vectibix (Panitumumab) Demonstrates Modest Improvement in CRC (Sept. 25/09)

Among patients with metastatic colorectal cancer, initial treatment with a combination of chemotherapy and Vectibix (Panitumumab) delays cancer progression by 1.6 months compared with chemotherapy alone. This benefit, which was reported at a major European cancer conference, only applied to patients whose tumors did not contain a mutation in the KRAS gene. Vectibix inhibits cancer cell growth and survival by targeting a protein known as the epidermal growth factor receptor (EGFR). Vectibix appears to benefit only those patients whose cancers do not contain a mutation in a gene known as KRAS. KRAS mutations occur in an estimated 40-50% of metastatic colorectal cancers and can be identified by testing a sample of tumor tissue. To evaluate the effectiveness of Vectibix in the **initial (first-line) treatment** of metastatic colorectal cancer, researchers conducted a Phase III clinical trial known as PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy). The study enrolled 1,183 patients. Study participants were assigned to receive treatment with FOLFOX chemotherapy alone or FOLFOX plus Vectibix.

- Among patients without KRAS mutations, the addition of Vectibix delayed cancer progression. Progression-free survival (time before cancer got worse) was **9.6 months** among patients treated with chemotherapy plus Vectibix compared with **8.0 months** among patients treated with chemotherapy alone.
- Among patients with KRAS mutations, the addition of Vectibix worsened outcomes. Progression-free survival was **7.3** months among patients treated with chemotherapy plus Vectibix compared with **8.8** months among patients treated with chemotherapy alone.
- Side effects of Vectibix included skin rash, low magnesium levels, and diarrhea.

The results of this study suggest that the addition of the targeted therapy Vectibix to first-line chemotherapy modestly improves progression-free survival (time before cancer got worse) among patients with metastatic colorectal cancer. The benefit of Vectibix only applies to patients whose tumors do not contain KRAS mutations.

Douillard J, et al. Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as 1st-line treatment (tx) for metastatic colorectal cancer (mCRC): the PRIME trial. Presented at the Joint ECCO 15-34th ESMO Multidisciplinary Congress. Berlin, Germany, September 20-24, 2009. Abstract 10LBA.

8. Avastin + Folfiri or Folfox in Chemo-refractory patients with mCRC (Sept. 29/09)

The anti-VEGF antibody bevacizumab, or avastin, associated with an irinotecan or oxaliplatin-based chemotherapy was proved to be superior to the chemotherapy alone in first or second line treatment of metastatic colorectal cancer (mCRC). However, it was reported to have no efficacy in 3rd or later-line, alone or with 5FU. The aim of this study was to evaluate the activity of bevacizumab combined with FOLFIRI or FOLFOX in mCRC who had failed prior chemotherapy (chemo-refractory) with fluoropyrimidine plus irinotecan and/or oxaliplatin. Thirty one consecutive patients treated between May 2005 and October 2006 were included in this retrospective study. All of them had progressed under a chemotherapy with fluoropyrimidine plus irinotecan and/or oxaliplatin and received bevacizumab (5mg/kg) in combination with FOLFIRI or simplified FOLFOX4 every 14 days. Ten patients (32.2%) had an objective response (1 Complete Response, 9 Partial Response) and 12 (38.8%) were stabilized. The response and disease control rates were 45.4% and 100% when bevacizumab was administered in 2nd or 3rd line and 25% and 55% in 4th or later line respectively. Among the patients who had previously received the same chemotherapy than that associated with bevacizumab (28 patients) the overall response rate was 35.7% and 39.3% were stabilized. Median progression free survival (PFS – time before disease got worse) and overall survival (OS) were 9.7 and 18.4 months respectively. Tolerance of bevacizumab was acceptable. This study suggests that bevacizumab combined with FOLFOX or FOLFIRI may have the possibility to be active in chemorefractory and selected mCRC patients who did not receive it previously.

Lievre, Astrid, et al., Bevacizumab plus folfiri or folfox in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study. BMC Cancer, 2009; Vol. 9, p.347.

9. Company Produces Monoclonal Antibodies Against CRC (Sep. 29/09)

MabCure Inc. a biotechnology company that has developed a series of highly specific monoclonal antibodies (MAbs) to combat various types of cancers, has developed MAbs against Colorectal Cancer (CRC) as well. The company plans to explore the use of these MAbs in terms of both the early diagnosis of CRC (in blood or feces specimens), as well as imaging agents for detecting micrometastatic disease during surgery and the detection of cancerous polyps during colonoscopy. The creation of MAbs against CRC allows MabCure to explore its uses for diagnosis and imaging in as timely a manner possible.

www.cancercompass.com/cancer-news/1,16364,00.htm

10. Erbitux + Folfiri or Folfox4 Aids mCRC Patients with Wild Type Kras Tumours (Sept. 29/09)

New research presented last month at a major European Oncology meeting has shown previously untreated patients who received the targeted cancer drug Erbitux(cetuximab) along with either FOLFIRI or FOLFOX4 chemotherapy lived up to 4 months longer than patients receiving just the chemotherapy. Patients had cancers showing a particular genetic make-up that responds well to treatment. The new findings came from combined results (a meta-analysis) of two studies - the large phase III CRYSTAL study and the smaller phase II OPUS study - in which over 1000 patients with advanced (metastatic) colorectal cancer in total participated. Both studies had investigated first-line therapy with and without Erbitux. The CRYSTAL study used a chemotherapy known as FOLFIRI consisting of infused 5FU, leucovorin and irinotecan; the OPUS study used a chemotherapy consisting of infused 5FU, leucovorin and oxaliplatin. In 845 of the patients, researchers were able to confirm whether patients' tumours had the wild-type KRAS gene, known to respond well to Erbitux, or a mutant KRAS gene which does not. Results showed adding Erbitux to the standard first-line chemotherapies mentioned above, gave a greater than two-fold increase in the chances of tumours responding, and significantly reduced the risk of disease worsening by over one third (34%). The time before this happened was increased by over one month. The risk of dying was reduced by 19%. Median survival for patients from the CRYSTAL study was 23.5 months for patients who added Erbitux to chemotherapy and 20 months for FOLFIRI alone. In the OPUS study median survival for patients who added Erbitux to FOLFOX4 was 22.8 months compared to 18.5 months for FOLFOX4 alone. Median survival, measured here as almost two years, means 50% of patients were likely to live beyond this time. Patients with metastases confined to the liver who respond to Erbitux and who are able to go on to have complete surgical removal of their liver tumours have the chance of being cured of bowel cancer.

www.medicalnewstoday.com/articles/165577.php

11. Topoisomerase I Associated with Irinotecan Efficacy (Sept. 30/09)

Thymidylate synthase (TS) and Topoisomerase I (Topo I) are significant biomarkers in colorectal cancer (CRC). This study examined the expression of TS and Topo I in patients with resected CRC who received adjuvant chemotherapy and determined if there was a correlation with the patient's outcome. All patients were diagnosed with CRC between 1989 and 2007 and treated with adjuvant chemotherapy. Tumor tissues were used for detection of TS and Topo I. The results were correlated with survival (OS) and disease free survival (DFS). 498 patients were included in the study. All patients received adjuvant 5-FU-based chemotherapy, 38% irinotecan-containing. Positive TS and Topo I expression was found in 43% and 48% of cases, respectively. Five-year OS was 74% and DFS was 68%. In multivariate analysis (term used for any statistical technique used to analyze data from more than one variable) Topo I expression was associated with a reduced risk of death. In the irinotecan-treated subgroup, those patients who expressed Topo I had a better OS. Researchers concluded that patients with resected CRC expressing Topo I seem to benefit from irinotecan-containing adjuvant chemotherapy. However randomized prospective trials are needed to confirm these results.

Kostopoulos, Ioannis, et al., Topoisomerase I but not thymidylate synthase is associated with improved outcome in patients with resected colorectal cancer treated with irinotecan containing adjuvant chemotherapy. BMC Cancer. 2009, Vol. 9, p.339.

12. Erbitux Use and Skin Rashes (Oct. 2/09)

Two studies showed that more colorectal cancer patients experience severe rash from erbitux than other cancer patients and significantly more men and younger people have severe rash than women and patients over 70. In the first study, although patients with a variety of cancers will develop skin rash from Erbitux (cetuximab) treatment, colorectal cancer patients are almost twice as likely to get a high-grade rash. Reviewing over 2,000 participants in 16 different trials, analysts found that 88% of patients develop some skin rash, with 11% having high-grade rashes. Almost 13% of colorectal cancer patients had the more severe high-grade rash compared to 6.6% of patients with other cancers. The second study showed that men and younger patients are more likely to develop a high-grade rash from Erbitux (cetuximab). In a review of a clinical trial of Erbitux in over 900 patients with colorectal cancer, 7% of men and 3% of women developed severe (grade 3) rash. 6% of patients under age 70 and 2% of older patients had severe rash.

Su, Xiao, et al., risk of High Grade Skin Rash in cancer patients treated with cetuximab – an antibody against epidermal growth factor receptor: Systemic Review and meta-analysis. International J for Cancer Research and Treatment: Oncology. Vol. 77, No. 2, 2009. pp. 124-133.
Green, Erin M, et al., Clinical Predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in North Central Cancer Treatment Group Study NO147. International J for Cancer Research and Treatment: Oncology. Vol. 77, No. 2, 2009. pp. 120-123.

13. Can Chemo Be Discontinued in Metastatic Colorectal Cancer? (Oct. 2/09)

This study compared chemotherapy discontinuation with maintenance therapy with leucovorin and fluorouracil (5FU) after six cycles of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy in the first-line treatment of metastatic colorectal cancer. 202 patients with untreated metastatic colorectal cancer were randomly assigned to receive six cycles of modified FOLFOX7 (mFOLFOX7) followed by simplified leucovorin plus bolus and infusional fluorouracil until progression **or** six cycles of mFOLFOX7 before a complete stop of chemotherapy (chemotherapy free interval = CFI). Reintroduction of mFOLFOX7 was scheduled after tumor progression in both groups. The primary study end point that was measured was duration of disease control (DDC – amount of time during which disease is under control). Median DDC was 13.1 months in patients assigned to the maintenance arm and 9.2 months in patients assigned to the CFI group. Median progression-free survival (PFS) and overall survival were 8.6 and 23.8 months, respectively, in the maintenance arm and 6.6 and 19.5 months, respectively, in the CFI arm. Median duration of maintenance therapy (arm 1) and CFIs (arm 2) were 4.8 months and 3.9 months, respectively. Overall response rates were 59.2% and 59.6% for the initial FOLFOX chemotherapy and 20.4% and 30.3% for FOLFOX reintroduction in arms 1 and 2, respectively. Researchers concluded **that the planned complete discontinuation of chemotherapy had a negative impact on DDC and PFS compared with the maintenance therapy strategy and therefore suggest that chemotherapy discontinuation cannot be decided before therapy is initiated in patients with advanced colorectal cancer.**

Tournigand, Christophe,et al., Can Chemo be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J of Clinical Oncology. JCO Early Release, published online ahead of print September 28, 2009, 10.1200/JCO.2009.23.4344.

14. Casopitant Prevents Nausea and Vomiting in Patients (Oct. 8/09)

The purpose of this phase III trial was to evaluate the efficacy and safety of regimens containing casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting during the first cycle in patients receiving moderately emetogenic (causing nausea) chemotherapy (MEC). Predominantly female patients (98%) diagnosed with breast cancer (96%) who were chemotherapy-naïve and scheduled to receive an anthracycline and cyclophosphamide (AC) – based regimen were enrolled into this multinational, randomized, double-blind, parallel-group, placebo-controlled clinical trial. All patients received dexamethasone 8 mg intravenously (IV) on day 1 and oral ondansetron 8 mg twice daily on days 1 to 3. Patients were randomly assigned to a control arm (placebo), a single oral dose casopitant arm (150 mg orally [PO] on day 1), a 3-day oral casopitant arm (150 mg PO on day 1 plus 50 mg PO on days 2 to 3), or a 3-day IV/oral casopitant arm (90 mg IV on day 1 plus 50 mg PO on days 2 to 3). The primary end point measured was the proportion of patients achieving complete response (no vomiting/retching or rescue medications) in the first 120 hours after the initiation of MEC. A significantly greater proportion of patients in the single-dose oral casopitant arm, 3-day oral casopitant arm, and 3-day IV/oral casopitant arm achieved complete response (73%, 73%, and 74%, respectively) versus control (59%;). The study did not demonstrate a reduced proportion of patients with nausea or significant nausea in those receiving casopitant. Researchers concluded that all casopitant regimens studied were more effective than the control regimen and casopitant was generally well tolerated.

Herrstedt, Jorn, et al., Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting inpatients receiving moderately emetogenic chemotherapy. J of Clinical Oncology. Published online ahead of print Oct. 5, 2009. DOI: 10.1200/JCOP.2009.21.8511.

15. Aspirin & Folic Acid Effecting Inflammation Markers for Colorectal Adenomas (Oct.12/09)

According to this study, inflammation markers do not appear to be involved with the chemopreventative (cancer preventing) effect of aspirin on colorectal adenomas. Aspirin has been shown to prevent the recurrence of colorectal polyps, but it's effects and mechanism of action are not clear. One hypothesis is that it may affect the levels of substances, such as C-reactive protein and others that are markers of inflammation. To study this, researchers examined changes in blood levels of five inflammation markers—**C-reactive protein, interleukin 6, tumor necrosis factor, soluble TNF receptor type II, and IL-1 receptor antagonist**—at baseline and at year 3 of 884 subjects. The trial had three aspirin groups (including an aspirin placebo group) and two folic acid groups (including a folate placebo group). Changes in levels of all five inflammation markers were not associated with adenoma recurrence. For those who did not receive folic acid, C-reactive protein levels in those in the 325 mg/day aspirin group changed very little, whereas it was statistically significantly increased in the placebo group. For subjects who received folic acid, the reverse association was observed. The data suggest that low dose aspirin has modest effects on stabilizing [C-reactive protein], which may be cancelled by a high level of folate. However, such beneficial effects do not appear to confer protection against colorectal tumours. Researchers concluded that “Inflammation markers do not mediate the previously observed effects of aspirin and folic acid on colorectal adenomas”.

Ho, Gloria Y F., et al., Antagonistic Effects of Aspirin and Folic Acid on Inflammation Markers and Subsequent Risk of Recurrent Colorectal Adenomas. J of the National Cancer Institute. Advance Access published online. Doi: 10.1093/jnci/djp346

16. Aspirin Reduces Risk of Developing New Polyps (Oct. 13/09)

Taking either high or low dose aspirin reduces the chances that people with colorectal polyps (*adenomas)* will develop more. A combined analysis of three randomized controlled trials that compared taking aspirin to a placebo after adenomas were removed found that people who took a daily low dose or baby aspirin had almost a 20% lower chance of discovering another adenoma during their next colonoscopy. High-dose or regular adult strength aspirin reduced risk of polyp recurrence by approximately 15%. Any aspirin reduced the risk of advanced adenomas by more than 35%. Advanced adenomas include polyps over 10 millimeters or polyps that are especially risky for developing into cancer including those with significant villous features, high-grade dysplasia (Dysplasia is the earliest form of pre-cancerous lesion recognizable in through a biopsy by a pathologist; it can be low grade or high grade and the high grade has a much higher probability of developing into cancer). In the three studies, over 2300 people with polyps on their initial colonoscopy were randomly assigned to aspirin or a placebo in the three studies, and 2,175 had a second colonoscopy to look for new polyps. Researchers concluded that this meta-analysis suggests that aspirin prevents recurrent colorectal adenomas among patients with a history of colorectal adenomas.

Gao, F., et al., The effect of aspirin in the recurrence of colorectal adenomas: a meta-analysis of randomized controlled trials. Colorectal Disease. Vol. 11, Issue 9, pp. 893-901.

SURIGCAL THERAPIES

17. Review of Colorectal Endoscopic Mucosal Resection (Sept. 25/09)

This study sought to evaluate the proportion of successful complete cure en-bloc (removed in one piece) resections of large colorectal polyps achieved by endoscopic mucosal resection (EMR). Studies using the EMR technique to resect large colorectal polyps were selected and reviewed. A successful complete cure en-bloc resection was defined as one piece margin-free polyp resection. 429 relevant studies were selected and subsequently reviewed by researchers. Data was taken from 25 studies. In the studies, the snares method was used to perform EMR. (Snares refers to a surgical instrument with a wire loop controlled by a mechanism in the handle, used to remove growths, such as tumors and polyps of the colon.) The rate of en-bloc resections leading to cure was 58.6% and researchers concluded that EMR is an effective technique for the resection of large colorectal polyps and offers an alternative to surgery.

Puli, SR, et al., Meta-analysis and systematic review of colorectal endoscopic mucosal resection. World J Gastroenterology, 2009 September. Vol. 15, No. 34: pp. 4273-4277.

18. Preoperative Multimodality Therapy Improves Outcomes in Rectal Cancer Patients (Sept. 28/09)

The standard treatment for operable rectal tumours has been chemoradiotherapy plus surgical resection of the tumour. Though, the optimal time to administer this therapy has not been clear. This study compared neoadjuvant (presurgical) versus adjuvant (post surgical) chemoradiotherapy in the treatment of locally advanced rectal cancer. Patients whose tumours were staged at T3 or T4 or node-positive rectal cancer were randomly assigned to preoperative or postoperative chemoradiotherapy. Chemotherapy consisted of fluorouracil (5FU) and leucovorin with radiation consisting of 45 Gy in 25 fractions with a 5.40-Gy boost within the original margins of treatment. In the preoperative group, surgery was performed within 8 weeks after completion of radiotherapy. In the postoperative group, chemotherapy began after recovery from surgery but no later than 4 weeks after surgery. The primary end points measured were disease-free survival (DFS – time before disease got worse) and overall survival (OS). From August 1993 to June 1999, 267 patients were included in the study. The analysis used data on 123 patients randomly assigned to preoperative and 131 to postoperative chemoradiotherapy. Surviving patients were observed for a median of 8.4 years. The 5-year DFS for preoperative patients was **64.7%** *v* **53.4%** for postoperative patients. The 5-year OS for preoperative patients was **74.5%** *v* **65.6%** for postoperative patients. A complete pathologic response was achieved in 15% of preoperative patients and no preoperative patient with a complete response had a recurrence. Researchers concluded **that preoperative chemoradiotherapy, compared with postoperative chemoradiotherapy, significantly improved DFS and showed a trend toward improved OS.**

Roh, Mark, et al., Preoperative Multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J of Clinical Oncology. Published online ahead of print Sept. 21, 2009. DOI: 10.1200/JCO.2009.22.0467

19. Perineural Invasion Can Predict Outcome in Colorectal Cancer Patients (Oct. 5/09)

Patients with node-negative (no lymph node involvement) colorectal cancer are not usually treated with chemotherapy. However, because many such patients nevertheless experience disease recurrence,

identification of factors associated with recurrence or poor outcomes may be useful in identifying which node-negative patients may benefit from adjuvant therapy (post surgical therapy). Tumor invasion of peripheral nervous system structures (perineural invasion) has been associated with worse prognosis and a more aggressive type of cancer. This retrospective study compared the prognostic significance of perineural invasion (PNI) in patients with node-negative and node-positive colorectal cancer. PNI was an independent predictor of worse outcome, including significantly reduced survival in node-negative patients. This finding suggests that PNI should be evaluated routinely and that node-negative, PNI-positive patients should receive adjuvant therapy. Most patients in this study had tumors of the rectum (27%), recto sigmoid (36%), or right colon (26%). PNI-positive tumors were present in 22% of patients. More rectal cancers than colon cancers were PNI positive (30% vs 19%). The presence of PNI was associated with known risk factors for poor outcome, such as more-advanced stage, higher grade, and presence of metastasis. Overall, researchers found the presence of PNI was associated with a doubling in risk of recurrence and of death from colorectal cancer. In node-negative patients, PNI-negative status was associated with significantly greater rates of 5-year survival (82% vs 29%) and of disease-free survival (56% vs 29%) than was PNI-positive status. Importantly, node-negative patients who were also PNI positive had worse 5-year overall survival rates than did node-positive patients (43% vs 67%). Based on these results, the researchers recommend including PNI status in pathology reports for colorectal tumors. In addition, they suggest that node-negative, **PNI-positive patients should be managed in a similar fashion as stage III patients and should receive adjuvant therapy.**

Liebig, C., et al., Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clinical Oncology. 2009 Sept. 8; Epub ahead of print.

20. Surgical Management of Colorectal Liver Metastases (Oct. 8/09)

This article nicely summarizes advances in surgical therapy for colorectal liver metastases, including a discussion of approaches used to convert patients with unresectable disease to resectable (using chemotherapy and portal vein embolization), techniques for surgical treatment of bilateral (involvement of both lobes of the liver) colorectal liver metastases, and advances and limitations of chemotherapy combined with surgery. The author is Dr. Eddie K. Abdalla, surgical oncologist at MD Anderson Cancer Center, in Houston, Texas.

Abdalla, Eddie, Surgical Management of Colorectal Liver Metastases. Community Oncology. Vol. 6, No. 8. pp. 349-357

21. Negative Lymph Node Count Is Associated with Survival of CRC Patients (Oct. 9/09)

The number of recovered lymph nodes is associated with good prognosis among colon cancer patients undergoing surgical resection. However, little has been known on prognostic significance of lymph node count. Among 716 colorectal cancers (stages 1–4), researchers examined patient survival in relation to the negative lymph node count (number of lymph nodes not affected by disease) and lymph node ratio (LNR = positively affected lymph nodes to total lymph node count). Compared with patients with 0–3 negative lymph nodes, patients with 7–12 and ≥13 negative nodes experienced a significant reduction in cancer-specific and overall mortality. The benefit associated with the negative node count was apparent across all stages, although the effect was significantly greater in stages 1–2 than stages 3–4 . In both stage 3 and stage 4, smaller LNR was associated with improved survival. Researchers concluded that **the negative lymph node count is associated with improved survival of colorectal cancer patients,** independent of other factors such as lymphocytic reactions to tumor and tumoral molecular features including MSI, CIMP, LINE-1 hypomethylation and *BRAF* mutation.

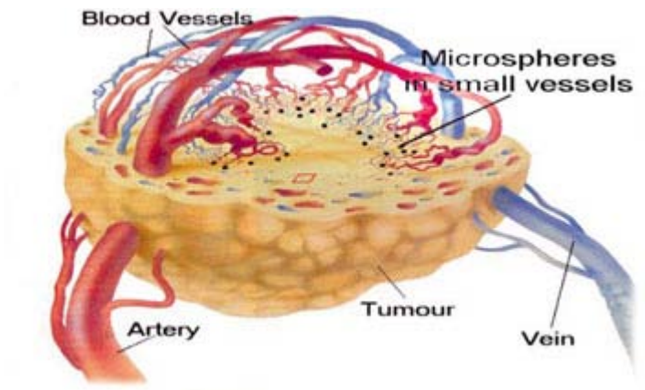
Ogino, S., et al., Negative Lymph node count is associated with survival of colorectal cancer patients, independent of tumoral molecular alterations and lymphocytic reaction. American J of Gastroenterology. 2009 Oct. 6. Epub ahead of print.

RADIATION / INTERVENTIONAL RADIOLOGY

22. New Clinical Trial For Treatment of Liver Mets from CRC (Sept. 18/09)

A multi-center, multi-national phase III clinical trial comparing the effectiveness of targeted radiation combined with folfox6 chemotherapy to chemotherapy alone as a first line treatment of colorectal cancer that has metastasized to the liver is under way in Europe, the US, Australia and New Zealand. It is called the **Sirflox** study. In the study, all patients will receive a standard chemotherapy regimen consisting of folfox6. Half of the patients will also undergo Selective Internal Radiation Therapy (sirt), a novel treatment that uses millions of microscopic radioactive beads to deliver high doses of radiation directly to the site of tumours (see image below). Because of the targeted delivery method, a much higher dose of radiation can be used to reduce the size and activity of tumors in the liver, while sparing healthy tissue. Those patients wishing to obtain more information about the sirflox trial and enrollment criteria may contact Marisabel Davalos, associate director of Clinical Research Programs for the Herbert Wiertheim College of Medicine at 305 654 3018. The use of Sirspheres is approved in the European Union, Australia and other countries. Sirspheres microspheres are indicated in the USA for the treatment of

unresectable metastatic liver tumours from primary colorectal cancer with adjuvant intra-hepatic artery chemo using floxuridine.



Source: ***http://www.mc.vanderbilt.edu/reporter/reporter_jpgs/reporter_11.08.02_1.jpg***

Selective Internal Radiation Therapy (SIRT) targets a very high radiation dose to tumors within the liver, regardless of their cell of origin, number, size or location. The procedure uses biocompatible radioactive microspheres that contain yttrium-90 and emit high energy beta radiation. The spheres are implanted using a catheter placed in the artery feeding the liver and travel via the blood stream, where the spheres are targeted to the tumors within the liver. The spheres are trapped in the small blood vessels of the tumor. Doctors do not have to identify the number or location of tumors, since the spheres target the cancerous growth in the liver. Once trapped within the tumor, the spheres destroy the tumor, without affecting most of the normal liver tissue.

www.sirtex.com

23. Whole Brain Radiotherapy After Surgery For Brain Mets (Sept. 25/09)

The role of prophylactic whole brain radiotherapy after either surgery or radiosurgery of brain mets is still debated in the literature. This phase III study demonstrated that whole brain radiotherapy (WBRT) after surgery or focused brain radiation to treat brain tumours that had spread into the brain from other cancer sites such as colorectal, did not improve either overall survival time or the time that patients were able to function independently. It did extend time before cancer got worse within the brain and prevented some deaths directly caused by pressure within the brain compared to patients who were only observed after their initial surgery.

Soffietti, R., et al., Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of 1-3 cerebral metastases – results of the EORTC 22952-26001 study. European J of Cancer Supplements, Vol. 7, No. 2, September 2009, page 494.

SCREENING

24. New Test Detects Stage I, II, and III Colon Cancers in Pre-Clinical Trials (Sept. 17/09)

EDP Biotech Corporation (EDP), a developer of immunodiagnostic tests for humans and animals, announced that its ColoMarker assay achieved 100% detection rate for colon cancers presented at stages I through III in pre-clinical trials. ColoMarker is the first assay (an assay is an analysis done to determine the presence of a substance and the amount of that substance. Thus, an assay may be done for example to determine the presence of a colorectal cancer biomarker in the blood of a person) of its kind to enable both early detection screening and patient management capabilities. ColoMarker could make accurate, early detection of colon cancer as easy as an additional blood test conducted as a routine part of patients' annual physicals, in much the same way Prostate-Specific Antigen (PSA) tests are used to screen for prostate cancer today. The assay would become the first to combine diagnostic applications with use as a patient management tool that could help physicians determine the effectiveness of colon cancer treatment in patients. The pre-clinical trials, conducted from January through August 2009, evaluated 2,370 freshly drawn blood samples. ColoMarker, which uses a proprietary biomarker developed by EDP, had an overall accuracy rate of 93%. When compared to the Fecal Occult Blood (FOB) test, the current clinical standard test recommended for colon cancer screening, ColoMarker performed extremely well. In a test panel of 243 samples drawn from patients who exhibited possible colon cancer and were referred to a specialist, the false positive rate was significantly lower for the ColoMarker assay (11%) than for the FOB assay (30%). Notably, the ColoMarker assay detected 100% of early-stage (Stage I) colon cancer; the FOB assay missed about 60%. The company is moving toward next steps for the commercialization of the test.

www.medicalnewstoday.com/articles/164201.php

25. New Blood Tests Developed For CRC Detection (Sept. 20/09)

Two new blood tests have been developed for the detection of colon cancer without the need for invasive procedures or unpleasant exams (one from Belgium and the other from Germany). The tests use blood samples to detect specific genetic signals of the disease and could help predict whether it is likely to spread. Higher levels of messenger RNA for the S100A4 gene were found in blood from pateitns with gastrointestinal cancers than in blood from healthy volunteers. Blood levels increased as cancer stage increased. Patients with cancer that had already spread had the highest levels. Patients whose cancer eventually spread, had higher blood levels of S100A4 mRNA when their blood was first tested, leading to a possible test to predict possible metastasis. German scientists collected blood samples from 466 patients with rectal, colon, or gastric cancer during their hospitalization and outpatient care. They also collected blood from 51 healthy volunteers. They analyzed the blood for the amount of messenger RNA for a gene known to contribute to the presence and spread of gastrointestinal cancers, the S100A4 gene. They found it in higher levels in the patients with cancer and even higher in those patients who had metastatic cancer. Before the test can be used as part of a screening program to find cancers before there are symptoms, it needs to be validated in a larger, prospective clinical trial, according to the research team.

Stein, U., et al., S100A4 transcripts in blood of colon, rectal and gastric cancer patients: development of a new blood-based assay for improved diagnosis and prognosis. European J of Cancer Supplements, Vol. 7, No.3, September 2009, page 9.

26. Early Stage Patients Should Receive Regular Follow-up (Sept. 21/09)

This study demonstrated that patients with very early stage colon cancer benefit as much from regular followup testing after surgery as later stage patients do. While overall patients with stage I or IIA colon cancer (early stage) have a lower risk of cancer returning than patients with stage IIB or III (later stage), careful surveillance after surgery was as effective in finding and treating cancer in both groups. About one in three patients in both the early and late stage who had a recurrence detected during surveillance were able to have surgery with the goal of curing their cancer. Researchers divided 872 patients without metastatic colon cancer into two categories:

- Early stage disease: stages I or IIA
- Late stage disease: stages IIB and III

All patients in the study, no matter their stage at diagnosis, followed the same surveillance plan after surgery which consisted of physical exams, CEA tests, chest x-rays, annual colonoscopies, and abdominal CTs. Of the entire group of 537 patients with an early stage diagnosis (stage I and IIA), 55 had a recurrence. 20 of them went on to a second surgery and had a median survival of 51 months after their operation. Those for whom surgery wasn't possible had a much shorter survival of approximately 9 months. There were 254 patients initially diagnosed as late stage (stage IIB and III). Of those, 91 experienced a recurrence and 32 were able to have a second surgery. Like the early stage patients, a second surgery led to much longer survival — 36 months versus 11 months without surgery. Researchers concluded that **patients with early-stage colon cancer have similar sites of recurrence, and receive similar benefit from post recurrence therapy as late stage patients; implementation of surveillance guidelines for early-stage patients was appropriate.**

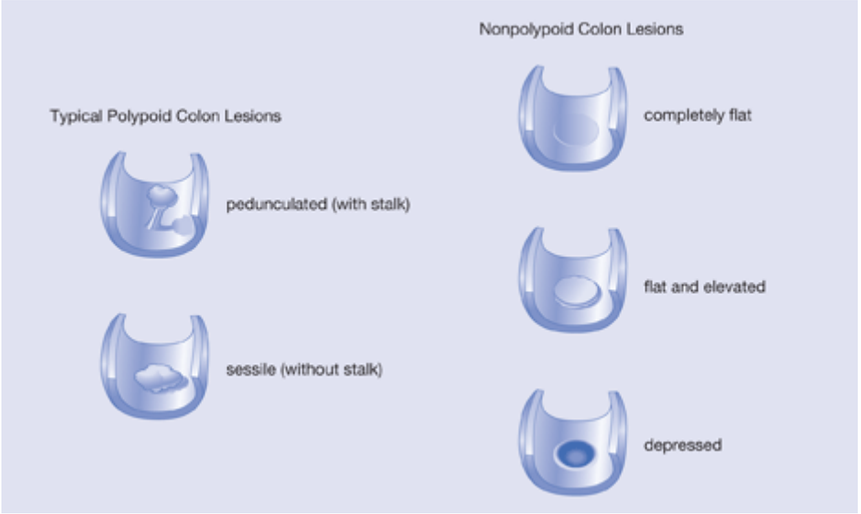
Tsikitis, Vassiliki, et al., Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. J of Clinical Oncology. Vol. 27, No. 22, 2009: pp. 3671-3676

27. The Detection of Flat Lesions (Sept. 28/09)

Regular colon cancer screening is the single best way to detect colon cancer early, when it's most treatable and most likely to be cured. During colon cancer screening, doctors will look for polyps, growths in the colon and rectum that if left untreated, may develop into cancer. While many polyps "stick out" from the wall of the colon and are easy to see, a new report from Johns Hopkins draws attention to a type of growth, or "lesion", in the colon that is **flat.** This means it does not rise above the surface of the inside of the colon, making it much harder to see. And if a pre-cancerous growth is not seen, it will not be removed. Fortunately, as the report points out, there are some steps you can take to improve the chances that your doctor can find, and remove, flat colon cancer growths. These include:

- Having your doctor go slowly when withdrawing the scope from your colon and rectum greatly improves the ability to see flat colon growths.
- Preparing for your colonoscopy exactly as prescribed. This means following instructions for what to do 1 week, 2 days, and 1 day before your scheduled colon cancer screening. Also be sure to know what you need to do the day of your screening, so your colon is clear and easy to see.
- Following up on any further testing that your doctor wants to perform.

- Paying attention to any symptoms that may signal colon cancer. Even if you've received a "clean bill of health" on your colon screening, you should pay attention to your body. Colon screening is very good at detecting colon cancer, but it is unfortunately not foolproof. Should you notice symptoms, inform your doctor.



Typical polyps have traditionally been characterized as growths that look like a cauliflower on a stalk (as labeled on the left hand side of the image above). But recent studies have identified lesions that are flat or even slightly depressed (as labeled on the right hand side of the image).
Source; http://www.johnshopkinshealthalerts.com/reports/colon_cancer/3165-1.html

http://www.johnshopkinshealthalerts.com/reports/colon_cancer/3165-1.html

28. Toronto Researchers Create Microchip For Detection and Severity of Cancer (Sept. 29/09)

U of T researchers have used nanomaterials to develop a microchip sensitive enough to quickly determine the type and severity of a patient's cancer so that the disease can be detected earlier for more effective treatment. Their groundbreaking work, reported Sept. 27 in *Nature Nanotechnology* heralds an era when sophisticated molecular diagnostics will become commonplace. The researchers' new device can easily sense the signature biomarkers that indicate the presence of cancer at the cellular level, even though these biomolecules – genes that indicate aggressive or benign forms of the disease and differentiate subtypes of the cancer – are generally present only at low levels in biological samples. Analysis can be completed in 30 minutes, a vast improvement over the existing diagnostic procedures that generally take days. The system developed by the Kelley/Sargent team is a revolutionary technology that can allow the tracking of biomarkers that might have significant relevance to cancer, with a combination of speed, sensitivity, and accuracy not available with any current technology

Kelley, Shana, et al., Programming the detection limits of biosensors through controlled nanostructuring. Nature Nanotechnology, September 27, 2009. Published online ahead of print. Doi: 10.1038/nnano.2009.276

PSYCHOSOCIAL

29. How Cancer Affects Mental Health (Sept.21/09)

One of the most challenging aspects of a cancer diagnosis is how it affects mental health. It's not surprising that receiving a cancer diagnosis would cause stress, anxiety, and in many cases depression. What is less clear is how these mental health issues may affect survival after diagnosis. A new study helps to answer this question and points to the importance of seeking help if diagnosed with cancer and are experiencing depression. The study assessed the extent to which depressive symptoms and major depressive disorder predict disease progression and mortality in cancer patients. The research published in the journal Cancer provides an excellent perspective at how depression may affect survival after a cancer diagnosis has been delivered. A process called meta-analysis was used to combine and analyze data from 25 previous studies. The advantage of this approach is that it allows for large numbers of people to be studied together. The more people in a study, the more likely it is that relationships between possible causes and effects will be discovered, if they exist. The results of the study did ***not*** find that depression or depressive symptoms affects progression of disease. However, cancer patients with depressive symptoms were **25%** more likely to die from any cause, including cancer, and patients diagnosed as having minor or major depression were **39%** more likely to die. The study also found that if a cancer diagnosis is followed with feeling overwhelmed, stressed, or depressed, there are many options to address these issues. There is no reason to suffer depression alone. Your health care team is the first place to start when seeking help to get mental health back on track. In addition to this, the following can help you get the support you require. If a patient is struggling to cope, the following are recommended

- **Acknowledge that it's normal to feel this way**
- **Tap into cancer survivor support groups**
- **Seek professional help**.
- **Don't be afraid of medication**
- **Keep in mind that this study does not conclusively prove cause and effect**
- **Find inspiration in the stories of others**

Satin, Jillian R., et al., Depression as a predictor of disease progression and mortality in cancer patients. Cancer. Published online September 14, 2009.

30. Improving Pain Relief in Cancer Patients (Oct. 9/09)

A pooled analysis of 21 studies of cancer pain found that talking to patients about how the strong pain medications worked, how best to take them, and myths about them improved patients' pain relief by a full point on a 10 point scale. In discussing the research at the United Kingdom's National Cancer Research Institute's Cancer Conference in Birmingham on October 7, Professor Michael Bennett said, *"Helping people manage pain is a major challenge for doctors and our research shows for the first time that education is an effective, easy and cheap way to do this."*

Hear an interview with Professor Bennett from NCRI.

Bennett, Michael, et al., Knowledge Boosts Pain Killing Drugs. National Cancer Research Institute Cancer Conference, UK. Abstract #2009, October 2009.

OTHER

31. Lymphocytes In/Near Tumours Predicts Better Outcomes for CRC Patients (Sept. 19/09)

This study demonstrated that an immune response in and around colorectal cancer tumors strongly predicts survival at any stage. When researchers in Paris found lymphocytes (white blood cells) infiltrating tumors or the lymphatic, blood vessel, or nerve tissue around the tumor, prognosis for surviving the cancer was very good. Low involvement of infiltrating lymphocytes predicted poor survival, even in early stages of the disease. Jerome Galon and his colleagues have developed a simple *immune score* which may help identify high-risk patients, particularly in early stages where it is often difficult to decide on whether to have chemotherapy or not.

Galon, J., et al., Intratumoral Immune Reaction: a novel paradigm for cancer. European Congress of Immunology. September 16, 2009: Berlin.

32. Younger Women With CRC Outliving Men (Sept. 29/09)

A new study suggests that estrogen or other hormones could help younger women with colorectal cancer live longer than men with the disease. Studies have been alluding to the fact that estrogen prevents colorectal cancer, but this is the first study to suggest it may improve outcomes once diagnosed with colorectal cancer. Lenz and colleagues examined medical records of 52,882 patients who had metastatic colorectal cancer over a 16-year period. Women age 18 to 44 years lived an average of three months longer than men -- 17 months versus 14 months. But the effect wasn't the same for older women. They survived for an average of seven months, compared to nine months for men. Lenz believes estrogen levels could be playing a role in patient outcome. Lenz maintained that further studies are warranted to determine the role of estrogen in colorectal cancer.

Lenz, Heinz-Josef, et al., Gender disparities in metastatic colorectal cancer survival. Clinical Cancer Research. 2009; Vol. 15, Issue 20: OF1-7.

33. Multidisciplinary Management of Stage IV CRC with Liver Mets (Sept. 29/09)

The management of stage IV colorectal cancer with liver metastases has traditionally involved a multidisciplinary approach. In the last several decades, there have been great strides made in the therapeutic options available to treat these patients with advancements in medical, surgical, locoregional and adjunctive therapies available to patients with colorectal liver metastases. As a result, there have been improvements in patient care and survival. Naturally, the management of colorectal liver mets has become increasingly complex in coordinating the various aspects of care in order to optimize patient outcomes. This study performs a review of historical and up to date literature wherein articles were utilized to examine relevant topics of interest in patients with colorectal liver mets including criteria for resectability, technical/surgical considerations, chemotherapy, adjunctive and locoregional therapies. This review explores the various disciplines and modalities to provide current perspectives on the various options of care for patients with colorectal liver mets. Improvements in modern day chemotherapy have allowed clinicians to pursue a more aggressive surgical approach in the management of stage IV colorectal cancer with colorectal liver mets. Additionally, locoregional and adjunctive therapies has

expanded the armamentarium of treatment options available. As a result, the management of patients with colorectal liver mets requires a comprehensive, multidisciplinary approach utilizing various modalities and a more aggressive approach may now be pursued in patients with stage IV colorectal cancer with colorectal liver mets to achieve optimal outcomes.

***Abdel-Misih, Sherif RZ, et al., Update and review of the multidisciplinary management of stage IV colorectal cancer with liver metastases. World Journal of Surgical Oncology* 2009, Vol. 7:72. doi:10.1186/1477-7819-7-72**

34. Research Shows that Colitis Can Turn to Cancer (Oct. 12/09)

University of Florida researchers have grown tumors in mice using cells from inflamed but noncancerous colon tissue taken from human patients, a finding that sheds new light on colon cancer and how it might be prevented. Scientists observed that cancer stem cells taken from the gastrointestinal system in patients with a chronic digestive disease called ulcerative colitis will transform into cancerous tumors in mice. The finding may help explain why patients with colitis have up to a 30-fold risk of developing colon cancer compared with people without the disease. Although colonoscopy is very effective in screening and preventing colon cancer for most people, for patients with colitis no diagnostic tests work well because the inflamed tissue makes identification of precancerous changes difficult. UF scientists gathered colitic tissue from humans and chemically screened it for colon cancer stem cells, also called tumor initiating cells. These cells were then isolated and monitored in mice to see if tumors would grow. Researchers claim these findings shed light on the fact that it may not be just the cancer "seed" cell, but the "soil" – in this case inflamed colon tissue – that plays a role in the development of cancer. The study emphasizes the emerging role of the surrounding inflammatory tumor microenvironment on tumor growth and subsequent metastasis. Researchers have identified a potentially important mechanism to explain why long-standing inflammation of the colon predisposes patients to the development of cancer. To further understand the role of the "seed" and "soil" interaction, UF researchers paired colon cancer stem cells with normal, colitic and cancerous human cells taken from the scaffolding layer of the large intestine. The cells were implanted into mice to analyze growth rates. The combination of tumor cells and normal scaffolding tissue cells grew at the slowest rate. Tumor cells paired with cancerous tissue grew at an intermediate rate, and tumor cells paired with the colitic tissue grew at the fastest rate. Researchers found heightened levels of two immune system hormones called interleukin-6 and interleukin-8 in the cells from the colitic and cancerous tissues, which had the faster growth rates. When UF researchers decreased the expression of these hormones within the cells, the tumor growth drastically decreased. When the hormones returned, the tumors began to grow again. Clinical trials looking at the role of one of these hormones in humans are under way in England

Huang, Emina H., et al., Aldehyde dehydrogenase-expressing colon stem cells contribute to tumorigenesis in the transition from colitis to cancer. Cancer Research. Published online first on October 6, 2009. doi: 10.1158/0008-5472

35. Biomarkers and Colorectal Cancer Survival (Oct. 13/09)

The changes in two genes that occur in some colorectal cancers can forecast chances for good or poor survival in colorectal cancer patients. Patients whose cancers had high microsatellite instability (MSI) had significantly better outcomes at every stage, but mutations in the KRAS gene predicted poorer survival. Microsatellite Instability refers to a change that occurs in the DNA of tumor cells in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell. Kras gene refers to a gene that may cause cancer when it is mutated (changed). The K-ras gene makes the KRAS protein, which is involved in cell signaling pathways, cell growth, and cell death (apoptosis). Agents that block the activity of the mutated K-ras gene or its protein (known as anti-EGFRs) may stop the growth of cancer.

Scientists assessed MSI and KRAS genetic mutations in 532 primary colorectal cancers removed during surgery. 12% of cancers had high levels of microsatellite instability (MSI), while 36% had mutations in the KRAS gene. MSI was more common in early stages with very little MSI in cancers diagnosed at stage IV where cancer had spread beyond the colon:

- stage I: 15%
- stage II: 21%
- stage III: 10%
- stage IV: 2%

KRAS mutations were more evenly distributed across stages:

- stage I: 36%
- stage II: 34%
- stage III: 35%
- stage IV: 40%

Patients with MSI were much less likely to die of cancer within five years of their diagnosis. More than 9 out of ten (92%) were alive five years later compared to 6 of 10 (59%) of those who didn't show MSI.

KRAS demonstrated the opposite effect. Mutations in KRAS led to poorer five year survival with 55% alive compared to 68% of patients with normal KRAS (*wild-type)*. The researchers noted that there was a group of stage I and II patients who had a particularly poor chance of living 5 years. Those patients didn't have MSI but did have KRAS mutations. Researchers concluded MSI and KRAS mutation provide fundamental genetic signatures influencing tumor behavior across patient subsets and stages of tumor development.

Nash, Garrett M., et al., Kras mutation and microsatellite instability: two genetic markers of early tumor development that influence the prognosis of colorectal cancer. Annals of Surgical Oncology. Published online October 8, 2009. doi: 10.1245/s10434-009-0713-0

NUTRITION & HEALTHY LIFESTYLE

36. Prevention of Colorectal Cancer (Sept. 19/09)

The aim of this study was to review the dietary, geographical and genetic factors in the causation and possible role in the primary prevention of colorectal cancer. Data from experimental and clinical studies and population screening programs were analyzed to determine the factors responsible for the cause of colorectal cancer. The role of dietary constituents, including the consumption of fat, red meat, fibre content, alcohol consumption, and other lifestyle issues, including obesity, lack of exercise and geographical variations in cancer prevalence were reviewed. The role of genetic and lifestyle factors in the cause of colorectal cancer is evident from the experimental, clinical and population-based studies. Dietary factors, including the consumption of fat, fibre, red meat and alcohol, appear to have a **significant influence** in this regard, according to the researchers. The role of micronutrients, vitamins, calcium may be relevant but remain largely unclear. Researchers concluded that there is ample evidence favoring the role of various dietary and lifestyle factors in the etiology (the science that deals with the causes or origin of disease, the factors which produce or predispose toward a certain disease or disorder) of colorectal cancer. Modification of these factors is an attractive option, which is likely to help in the primary prevention and reduced disease burden.

Qasim, A., et al., Primary prevention of colorectal cancer: are we closer to reality? European J Gastroenterology Hepatology. September 19, 2009. Published online.

37. Consumption of Acrylamide May Cause Health Problems (Sept. 21/09)

Starchy fried foods can contain a chemical called acrylamide is quietly raising concern as a potential human carcinogen. A natural byproduct of cooking high-carbohydrate foods at high temperatures, acrylamide also turns up in a wide variety of roasted and baked foods, including breakfast cereal, baby food, bread and crackers. Previously known as a synthetic substance found in plastics, grouts and cigarette smoke, acrylamide exploded on to the food safety scene in 2002 when scientists at the Swedish Food Administration detected surprisingly high levels of it in high-carbohydrate foods and published evidence linking it to cancer in lab rats. But widely anticipated research to be released later this year is expected to confirm that megadoses of the chemical are carcinogenic in laboratory animals. It's the product of a chemical reaction that can occur in cooking. Acrylamide forms when sugars and an amino acid called asparagine are heated together at high temperatures - more than 248 degrees Fahrenheit. This effect, part of what's called the "Maillard reaction," enhances a food's color, flavor, aroma and texture. Among foods, the highest levels of acrylamide turn up in french fries and potato chips. But it also has been found in baked goods, coffee, cocoa, roasted asparagus and even canned olives. So far, studies have failed to find a link between the consumption of acrylamide-rich foods and the occurrence of colon, kidney or bladder cancers but the expectation of widely anticipated research is expected to confirm that megadoses of the chemical are indeed carcinogenic.

www.cancercompass.comcancer-enews/1,16316,00.htm

38. Number of Obesity-related Cancers Increasing (Sept. 24/09)

Obesity is increasingly being recognized as a risk factor not only for cancer development, but also for worse outcomes after cancer treatment. Links between obesity and endometrial cancer, postmenopausal breast cancer, and **colorectal cancer** are well established, but the effects of obesity appear to extend to several other types of cancer as well. According to the results of this large study conducted by the American Cancer Society, women with the highest BMIs were more likely than women with a healthy BMI to die of cancers of the gallbladder, pancreas, kidney, cervix, and ovary, as well as non-Hodgkin's lymphoma. The researchers estimated that 90,000 cancer deaths per year could be prevented if Americans maintained a healthy weight. BMI is a commonly used measure of body size. It involves a comparison of weight to height (weight in kilograms divided by height in meters squared). A BMI between 18.5 and 24.9 is generally considered healthy, a BMI between 25 and 29.9 is considered overweight, and a BMI of 30 or higher is considered obese. To explore the impact of excess body weight on cancer trends in Europe, researchers collected information from a number of different sources including the World Health Organization and the International Agency for Research on Cancer. Excess body weight was defined as a BMI of 25 or higher.

- In 2002, as estimated 70,000 cancer diagnoses in Europe were due to excess body weight.
- By 2008, this number was projected to be more than 124,000. Excess body weight accounted for 3.2% of all new cancer diagnoses in men and 8.6% of all new cancer diagnoses in women.
- Endometrial (uterine) cancer, postmenopausal breast cancer, and **colorectal cancer** were the most common weight-related cancers. These three cancer types accounted for 65% of all cancers due to excess body weight.

The researchers note that these estimates are conservative, and that the actual number of obesity-related cancers is likely to be higher. According to Dr. Andrew Renehan, the lead author of the study, "As more people stop smoking and fewer women take hormone replacement therapy, it is possible that obesity may become the biggest attributable cause of cancer in women within the next decade."

Renehan A. Obesity and overall cancer risk. Presented at the Joint ECCO 15-34th ESMO Multidisciplinary Congress. Berlin, Germany, September 20-24, 2009. Abstract I-327.

39. Diet Directly Connected to Colorectal Cancer (Oct. 2/09)

In this study, researchers analyzed data from 1,905 participants in the US Polyp Prevention Trial examining the effects of following a dietary intervention on polyp recurrence in people with prior history. Researchers monitored the effects of a low-fat, high-fiber, and high-fruit-and-vegetable diet on polyp recurrence over a four year period using food frequency questionnaires and colonoscopy screening tests. People who strictly followed the prescribed diet had 35% reduced odds of any polyp recurrence and 50% reduced odds of multiple or advanced recurrence compared with people who didn't follow a dietary intervention (control group). There was no difference in recurrence between people who had poor compliance with the diet and the control group. These results suggest that consistent adherence to a low-fat, high-fiber, and high-fruit and [high]-vegetable diet may be effective in preventing recurrence of colorectal adenomas and possibly in preventing colorectal cancer. Researchers concluded that eating healthfully may prevent the return of growths known as adenomatous polyps that increase the risk of colon cancer and suggest that strictly following a low-fat, high-fiber, and high-fruit-and-vegetable diet may prevent the return of polyps by as much as 35%.

Sansbury, Leah, et al., The effect of strict adherence to a high-fiber, high-fruit and –vegetable, and low-fat eating pattern on adenoma recurrence. Amer J of Epidemiology. Vol. 170, No. 5: pp. 576-584

40. Diet Supplements & Colorectal Cancer Markers (Oct. 8/09)

According to this study, the use of prebiotic, probiotic, and synbiotic dietary supplementation leads to changes in fecal microflora but not to variables associated with colorectal cancer. Gut microorganisms are a critical aspect of health and this study showed how gut microorganisms could be changed by taking a probiotic with a fiber supplement. But, researchers claim they still have much to learn about the relationship between gut microorganisms and important digestive diseases, such as bowel cancer and inflammatory bowel disease. This study consisted of a randomized crossover trial of supplementation with resistant starch and Bifidobacterium lactis. This was given alone or as a combined synbiotic preparation to 20 volunteers. The aim was to determine the effects on biomarkers of colorectal cancer. In the 17 subjects who completed the study, the team found that the synbiotic intervention generated a significantly different fecal stream bacterial community than did either the prebiotic or the probiotic intervention alone. However, there was no significant alteration in any other fecal, serum, or epithelial variables. Nevertheless, the researchers concluded that "even in the absence of other significant luminal events, the mechanisms underlying the microbial consequences of symbiotic interventions are worth exploring, particularly with regard to their implications for early colorectal carcinogenesis".

Worthley, DL., et al., A human, double-blind, placebo-controlled, crossover trial of prebiotic, probiotic, and symbiotic supplementation: effects on luminal, inflammatory, epigenetic, and epithelial biomarkers of colorectal cancer. American J Clinical Nutrition. 2009; Vol. 90:pp. 578-586.

41. Quercetin & Reduction in Colorectal Cancer (Oct. 14/09)

Diets rich in flavonoids may reduce the risk of developing colorectal cancer. Flavonoids are widely distributed in foods of plant origin. **Quercetin** is one of a number of water-soluble plant pigments called bioflavonoids. Quercetin and the other bioflavonoids cannot be synthesized by humans. However, they reportedly exert a wide variety of biological effects when ingested. It has been shown to have anti-inflammatory and antioxidant properties, and is being investigated for a wide range of potential health benefits. Quercetin is found in many foods including apples, onions, tea, berries, grapes, broccoli, cauliflower, and cabbage, as well as many seeds and nuts. This study has found that increased intakes of the compound quercetin may reduce the risk of developing colon cancer by 50%. Researchers conducted a case-control study involving 264 people with confirmed colorectal cancer and 408 healthy, cancer-free controls whose objective was to evaluate any independent associations of total dietary intake of four flavonoid subclasses and the risk of developing colorectal cancer in a tea-drinking population with a high colorectal cancer incidence.. Using a food frequency questionnaire, researchers were able to calculate flavonoid intake. They determined that although no association was found between developing colorectal cancer and total daily flavonol intake, there was an inverse association between **non-tea flavonol** and colorectal cancer risk. When the researchers considered only flavonoids from non-tea sources and the specific site of the cancer, a significant protective effect was documented for non-tea

flavonols, specifically, **quercetin** and colon cancer but there was no protective effect for rectal cancer. Therefore, the authors concluded that quercetin appears to reduce the risk of developing colon cancer.

Kyle, Janet A.M., et al., Dietary flavonoid intake and colorectal cancer: a case-control study. British J of Nutrition. Published online September 2009. doi: 10.1017/S0007114509991784

42. Color of Fruits & Vegetables Offer Health Benefits (Oct. 1509)

Color of fruits and vegetables appears to be helping prevent certain ailments. Fruits and vegetables contain phytochemicals which are packed with vitamins and minerals. They can protect against the effects of aging, cancer and heart disease. Fruits and vegetables are categorized by color. These categories can help alert the healthy consumer of what benefits the fruit or vegetable can confer. These color categories include red, blue/purple, yellow/orange, white and green. Those in the **white** category, such as bananas, garlic, onions and potatoes, help with heart health, lowering cholesterol and reducing the risk of some cancers. Cantaloupes, mangoes and sweet potatoes are all part of the **yellow/orange** category and help with the eye and heart health. **Green** grapes, kiwis, broccoli and spinach also help with vision and reducing the risk of cancer. Blueberries have the phytochemical anthocyanin which helps reduce age effects. A site created by the Centers for Disease Control and Prevention, which can be found at www.fruitsandveggiesmatter.gov, considers age, gender and activity level to measure how many cups of "fruits and veggies" one needs in a day. Securing a healthy variety means thinking color. Eating fruits and vegetables of different colors gives the body a wide range of valuable nutrients. Compared with people who consume a diet with only small amounts of fruits and vegetables, those who eat more generous amounts as part of a healthful diet are likely to have reduced risk of chronic diseases, including stroke and perhaps other cardiovascular diseases, and certain cancers, such as colorectal.

www.cancercompass.com/cancer-news/1,16423,00.htm