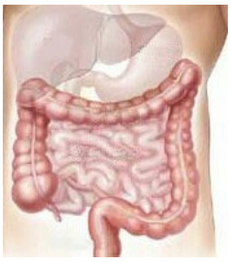
COLORECTAL CANCER RESEARCH
Month Ending June 19, 2009



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

ENCOURAGING

Dramatic Increase in Metastatic Colon Cancer Survival (May 26/09)

Novel chemotherapy and biological agents for metastatic colorectal cancer, combined with surgical advances in liver resection, have resulted in a dramatic increase in survival for patients with advanced disease, according to researchers at The University of Texas M. D. Anderson Cancer Center. It is the first study in the last 20 years to examine the survival rates for metastatic colorectal cancer, and finds that the median overall survival is now more than 30 months, compared to eight months for patients diagnosed before 1990. Five-year survival of patients diagnosed with the disease after 2004 is more than 30%. Over the past decade, the concept that specific metastatic liver lesions could be surgically removed has become more widely accepted as practice. Thus, more emphasis is now placed on identifying candidates for resection of their liver metastases. In the study, researchers found not only a significant improvement in overall survival for metastatic colorectal cancer patients, but also demonstrated that the degree and rapidity of the improvement is of a magnitude that is rarely seen in metastatic cancers. Many of these patients are not necessarily disease-free, but living with their cancer with a high quality of life. For some patients, the goal of making metastatic colorectal cancer a chronic condition is closer to becoming a reality. Looking at when these changes in colon cancer survivorship occurred, the study showed two distinct time periods that reflect the impact of both **hepatic resections** and the **availability of new novel therapies**. Beginning in 1998 and even more by 2000, physicians started performing higher volumes of hepatic resections, and that coincides with the initial increase in survival. The second stage of improvement began around 2004, simultaneous to the approval of many more chemotherapy and biological agents - cetuximab, bevacizimab, and oxaliplatin.

www.newswise.com/articles/view/52690

DRUGS / SYSTEMIC THERAPY

1. **Alpha Vax Announces Enrollment in Phase I/II Study of Active Immunotherapy in Patients with Metastatic Cancer** (May 14/09)

AlphaVax announced the completion of enrollment in a Phase I/II CEA cancer immunotherapy study being conducted by the Duke University Comprehensive Cancer Center in Durham, NC. This Phase I/II study is an open-label, dose-escalation study to evaluate the safety and immunogenicity of carcinoembryonic antigen (CEA(6D))-expressing virus-like replicon particle (VRP) immunotherapy in patients with advanced or metastatic CEA-expressing malignancies such as colorectal cancer. CEA is tumor protein found on many types of cancer including colorectal, pancreatic, gastric, breast, ovarian, and lung. The Phase I study consists of a dose escalation (increase) at 3 dosage levels of CEA-expressing VRP and the Phase II component has additional patients at the maximally tolerated dose. CEA-expressing VRP was administered by intramuscular injection every 3 weeks for a minimum of 4 immunizations, with additional doses in patients without progressive disease every 3 months. 24 patients have been enrolled targeted for this study, and while this is obviously not the size or kind of study upon which conclusions can be drawn, it appears to have a favorable tolerability and safety profile which will need to be much more fully evaluated in larger clinical trials.

www.cancercompass.com/cancer-news/1,15704,00.htm

2. **Antiviral Drug Ribavirin Shows Promise in 30% of Cancers** (May 17/09)

According to a large clinical trial conducted in Canada, a commonly used antiviral drug shows promise for treatment of 30% of cancer types. The antiviral drug **ribavirin** is shown to be effective for suppressing gene dysregulation (the interruption of normal gene expression) in patients with prostate, breast, **colon,** stomach, head and neck cancer. University of Montreal's lead investigator Dr. Borden found that ribavirin suppresses activity of the eIF4E gene, which is dysregulated in 30% of cancers, including colorectal. The results show much promise for cancer treatment, and the study is considered ground breaking.

The study shows that ribavirin dramatically improves outcomes in patients, including partial and complete cancer remission. Researchers studied the effects of ribavirin on patients with acute myeloid leukemia who had failed other treatments which resulted in striking clinical improvements with even partial and complete remissions. The next challenge is to combine the promising antiviral drug with chemotherapy to improve its effectiveness, and combat the development of resistance to the drug. Combining chemo with the antiviral drug ribavirin may result in complete remission in 30% of cancers.

Borden, Katherine, et al., Molecular targeting of the oncogene eIF4E in AML: a proof of principle clinical trial with ribavirin. Blood Journal. Published online ahead of print May 11, 2009.

3. Celebrex & Colon Cancer Prevention (May 18/09)

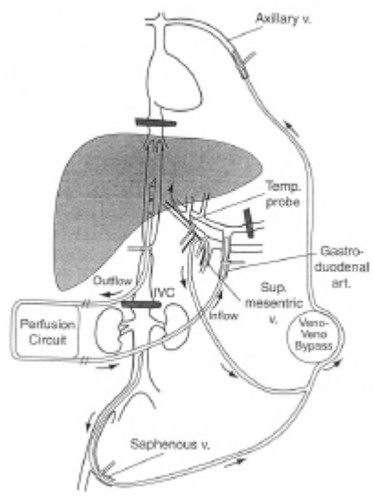
A new study finds that individuals who have low expression of the "Celebrex gene," 15-PGDH, are actually resistant to Celebrex treatment when used to prevent colon cancer. These findings suggest that measurement of 15-PGDH may identify which individuals are most likely to benefit from treatment with Celecoxib as a colon tumor preventative. And second, they suggest that identifying drugs that could increase 15-PGDH expression in the colon could be a potent new strategy for preventing development of tumors in the colon. In the Adenoma Prevention with Celecoxib (APC) trial, designed to test Celecoxib for the prevention of sporadic colorectal adenomas, the researchers showed that Celecoxib (brand name Celebrex, a Cox-2 inhibitor that relieves pain and inflammation without harming the digestive tract) treatment of individuals who had previously developed colon adenomas cut the rate of developing new adenomas by one-third, and cut the rate of developing new large adenomas by two-thirds. Some individuals, however, proved resistant to Celecoxib treatment and developed new colon tumors even while on the drug. Colon adenomatous polyps are benign tumors that are the immediate precursors of colon cancers. Previous studies (December 2004 and July 2006) discovered that the gene 15-PGDH is expressed by the normal colon and acts similarly to Celecoxib in preventing colon tumors by inhibiting the COX-2 pathway. The current study leads the researchers to ask, could protection from colon tumors by Celecoxib actually require the joint action of both the drug and the 15-PGDH gene? To answer the question the investigators examined mice that genetically lacked the gene 15-PGDH. In these mice, Celecoxib proved unable to prevent the development of colon tumors, suggesting that **both the drug and the gene are needed** to protect the colon from tumor development. The investigators then examined colon biopsies from human patients who had participated in the APC trial of Celecoxib. They found that among these individuals, colon 15-PGDH levels varied by 12-fold from lowest to highest. Most importantly, they found that the patients who were resistant to Celecoxib and had developed new colon tumors were all individuals who had low levels of colonic 15-PGDH. Thus in both mice and humans, Celecoxib works to prevent colon tumors only if levels of colonic 15-PGDH are high, while low levels of 15-PGDH leads to Celecoxib resistance.

Markowitz, Sanford, et al., 15-Hydroxyprostaglandin dehydrogenase inactivation as a mechanism of resistance to Celecoxib chemoprevention of colon tumours. PNAS: Published ahead of print May 22, 2009. doi: 10.1073/pnas.0902367106. PNAS June 9, 2009; vol. 106 #23; pp 9409-9413.

4. Isolated Hepatic Perfusion for Unresectable Liver Mets from Colorectal Cancer (May 20/09)

This study focused on ***hyperthermic isolated hepatic perfusion (IHP)*** in patients with unresectable liver mets from colorectal cancer with particular focus on IHP's usefulness as a second line option for patients whose tumors had progressed following combination systemic chemo treatment. Hyperthermic isolated hepatic perfusion is a procedure in which a catheter is placed into the artery that provides blood to the liver. A second catheter is placed into the vein that takes blood away from the liver. This temporarily separates the liver's blood supply from blood circulating throughout the rest of the body and allows high doses of heated anticancer drugs to be directed to the liver only. In this study, the drug of choice was melphalan, an anticancer drug used in the treatment of multiple myeloma as well as some other cancers. Hepatic arterial infusion (HAI) with floxuridine was also started 6-8 weeks post IHP in 46 of the 120 patients. Researchers concluded that IHP resulted in tumor shrinkage and prolonged survival in patients with colorectal cancer liver mets. Median overall survival was 17.4 months and 2 year survival was 34%.

For a schematic representation of hyperthermic isolated hepatic perfusion, please see diagram below.



Schematic representation of hyperthermic Isolated Hepatic Perfusion. Source: http://www.ncbi.nlm.nih.gov/bookshelf/picrender.fcgi?book=eurekah&part=A52000&blobname=ch375f5.jpg

Alexander, H Richard, et al., Analysis of factors associated with outcome in patients undergoing isolated hepatic perfusion for unresectable liver metastases from colorectal cancer. Annals of Surgical Oncology. Vol 16; Number 7, July 2009. pp1852-1859.

5. Ice Chips During Chemo Reduce Oral Mucositis Severity (May 20/09)

Cryotherapy (exposure of tissue to extreme cold) before, during, and after chemotherapy significantly decreased **oral mucositis** (inflammation of the tissues that line the mouth) severity and mucositis-related pain, compared with oral self-care alone, in a pilot study of multiple myeloma patients undergoing autologous stem cell transplantation. Prisco Salvador of University Health Network/Princess Margaret Hospital site in Toronto presented the study results at the Oncology Nursing Society 34th Annual Congress. The study group sucked on ice chips for 5 minutes before chemotherapy, 30 minutes during their infusion, and 25 minutes afterward, and were instructed in oral self-care, whereas the control group performed oral self-care only. All patients were symptom free on day 1 to day 5; lesions began to appear on day 6, peaked at day 9, and started to heal by day 12. Patients in the control group began having pain earlier according to lead investigator. At day 6, cryotherapy patients reported no oral mucositis pain, compared to control group. Only 8.7% of cryotherapy patients reported pain at day 9, compared with 41% of controls.

NB: Mucositis can result in colorectal cancer patients undergoing therapy with 5FU as well as other chemos.

www.oncologystat.com/news-and-viewpoints/news/Ice_Chips_During_Chemo_Reduce_Oral_Mucositis_Severity.html

6. Estrogen and Colorectal Cancer (May 20/09)

The Women's Health Initiative (WHI) is a long-term study, begun in 1991, that was designed to answer basic questions about women's health. The study has examined a wide variety of topics including hormone replacement therapy (HRT), diet and nutrition, heart disease, cancer, and osteoporosis. One component of the study examined how HRT in post-menopausal women may affect disease risk. New results from the WHI research recently were published, adding to the accumulating data that hormone replacement therapy is **not** effective for preventing most types of cancer, including colon cancer. Researchers had hoped that hormone replacement therapy may provide some benefit to aging women, by reducing colon cancer risk, but the research proved otherwise. Neither estrogen only nor estrogen plus progestin types of HRT reduced or increased the risk of colon cancer. At this point, it appears that HRT is not a good way for women to reduce colon cancer risk. If you are taking HRT, this study does not provide a reason to stop taking it. However, if you are taking HRT with the specific hope of decreasing colon cancer risk, you should talk to your doctor about whether it is worth it for you to do so.

Prentice, Ross L., et al., Colorectal Cancer in Relation to Postmenopausal estrogen and estrogen plus progestin in the women's Health Initiative clinical trial and observational study. Cancer Epidemiology, Biomarkers & Prevention. 2009: 18 (5): 1531-1537

7. Addition of Oxaliplatin to Chemo Improves Stage II and III Colon Cancer Outcomes (May 22/09)

According to this study, the addition of Eloxatin (oxaliplatin) to adjuvant (post-surgery) chemotherapy with fluorouracil (5FU) and leucovorin improves survival among patients with Stage II or Stage III colon cancer. To evaluate the effectiveness of Eloxatin in combination with 5-FU/LV among patients with Stage II or Stage III colon cancer, researchers conducted a Phase III clinical trial known as MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer). The study enrolled 2,246 patients. After surgery, patients received six months of

chemotherapy with either 5-FU/LV or Eloxatin/5-FU/LV. The combination of Eloxatin and 5-FU/LV that was evaluated in this study is also known as FOLFOX4. The results were as follows:

- 5-year survival without cancer recurrence was **73.3%** among patients treated with FOLFOX4 compared with **67.4%** among patients treated with 5-FU/LV alone.
- 6-year overall survival was **78.5%** in the FOLFOX4 group compared with **76%** among patients treated with 5-FU/LV alone. The survival benefit among patients treated with FOLFOX4 appeared to be limited to patients with Stage III cancer.

The researchers concluded that adding Eloxatin to 5-FU/LV significantly improved both disease-free survival (time before cancer got worse) and overall survival in this study of patients with Stage II or Stage III colon cancer. They note that this treatment combination should be considered after surgery for patients with Stage III colon cancer. Another chemotherapy combination that has been evaluated in the adjuvant setting is Camptosar (irinotecan) plus 5-FU/LV. In a separate study published in the same issue of the *Journal of Clinical Oncology*, **Camptosar (Irinotecan) plus 5-FU/LV was no more effective than 5-FU/LV alone**

Andre, T, et al., Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J of Clinical Oncology (early online edition). May 18, 2009.

Van Cutsem, E, et al., Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J of Clinical Oncology (early online edition). May 18, 2009.

8. Medical Marijuana as a Therapeutic Agent (May 23/09)

An article, by two researchers from the University of Naples, covers the potential benefits of cannabinoids in illnesses involving intestinal inflammation (e.g. Crohn's disease) and in colorectal cancer. The authors explain that "cannabinoids exert important physiological and pathophysiological actions in the digestive tract, including appetite regulation, emesis (nausea), protection of the gastric mucosa, intestinal ion transport, gastric emptying and intestinal motility." They then go into a detailed and highly technical explanation of how the body's CB1 and CB2 receptors — the route through which marijuana and the body's own marijuana-like chemicals act — are involved in controlling the excessive inflammation that is the hallmark of Crohn's and other forms of inflammatory bowel disease and how enhancing those actions can help. The researchers then go into a similarly detailed discussion of the cellular mechanisms by which cannabinoids — including natural plant cannabinoids like THC and CBD — fight colorectal cancer, opening the discussion with this: "Cannabinoids exert antiproliferative, antimetastatic and apoptotic actions in colorectal carcinoma epithelial cells as well as antitumoural effects in experimental models of colon cancer." The study appears to present some sound evidence for the use of the agent in the proper setting.

Izzo, Angelo, et al., Cannabinoids in Intestinal Inflammation and Cancer. Pharmacological Research. Published ahead of print. 2009. doi: 10.1016/j.phrs.2009.03.008

9. Impact of Older Age on the Efficacy of Newer Adjuvant Therapies in Patients with Stage II/III Colon Cancer (May 27/09)

Prior studies have suggested that older and younger patients with colon cancer receive similar benefit from intravenous FU adjuvant (post surgical) therapy. Combination and/or oral FU therapy are increasingly given as adjuvant therapy. This study sought to determine the impact of patients' age (less than 70 years and greater than 70 years) on colon cancer recurrence and mortality from adjuvant therapy with these newer options. Patients less than 70 years of age and patients greater than 70 years of age were assigned combinations of either irinotecan, oxaliplatin or oral FU (capecitabine) all having stage II/III colon cancer. Overall survival, disease free survival and time to recurrence were statistically significantly improved for those patients in the experimental vs. control arms among patients who were less than 70 years old, but not those older than 70 years. The results showed that patients greater than 70 years of age did not receive the same benefit from combination and or oral FU as those less than 70 years of age in respect of overall survival, disease free survival and time to recurrence. Researchers found that adding chemotherapy agents such as oxaliplatin or irinotecan to the standard 5FU regimen in older patients after surgery did not provide the benefits that younger patients saw. For the older patients, this meant that it was appropriate to choose the better tolerated treatment strategy of 5FU alone. At this point, researchers can only speculate as to why older patients did not benefit from combined chemotherapies.

McCleary, NA Jackson., et al., Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients with stage II/III colon cancer: Findings from the ACCENT Database. J Clinical Oncology. 27:15s, 2009. Abstract 4010 – 2009 ASCO Annual Meeting.

10. Gastrointestinal Perforation in Patients Treated with Avastin (May 28/09)

Gastrointestinal perforation is a potentially serious side effect of the targeted therapy Avastin (bevacizumab) which occurs in a very small percentage of the treated population. To explore how frequently this side effect occurs, this study evaluated information from 17 clinical trials. The results indicate that Avastin users are roughly twice as likely as nonusers to experience gastrointestinal

perforation but that the risk appears to vary by Avastin dose and tumor type. Gastrointestinal perforation refers to a hole that develops through the wall of the stomach, small intestine, colon, or gallbladder. The condition is potentially life-threatening. A link between Avastin and gastrointestinal perforation has been reported, and the prescribing information for Avastin recommends that Avastin be discontinued in patients who experience the condition. To explore how frequently gastrointestinal perforation occurs among patients treated with Avastin, researchers examined information from 17 clinical trials. These clinical trials enrolled a total of more than 12,000 patients. Here are the results:

- Gastrointestinal perforation occurred in slightly **less than 1%** of patients treated with Avastin. Among Avastin-treated patients who developed the condition, 21.7% (roughly one in five) died.
- Compared with patients who did not receive Avastin, patients who were treated with Avastin were roughly twice as likely to develop gastrointestinal perforation. Risk appeared to be greater at higher doses of Avastin and for patients with colorectal cancer or renal (kidney) cancer.

These results confirm that Avastin increases the risk of gastrointestinal perforation. Most patients treated with Avastin will not develop this condition, but when it occurs it can be life-threatening.

Hapani, S, et al., Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncology (early online edition). May 25, 2009.

11. Antineoplaston Therapy Doubles 5-Year Survival Rate Following Curative Resection of Hepatic Mets (May 27/09)

Positive results were borne from a phase II clinical study of **Antineoplaston therapy** (ANP therapy) in metastatic colon cancer following curative resection of liver mets. The study was performed in Japan. The study consisted of 65 colon cancer patients who had undergone curative resection of their liver mets and were randomized to one of the following groups:

1. intrahepatic infusion of 5FU
2. intrahepatic infusion of 5FU plus IV ANP therapy given (a) daily for seven days following hepatic resection, and (b) ANP therapy given orally daily for one year

There was a significant difference in overall survival between the 2 groups, with the 5 year survival rate in the 5FU plus ANP therapy arm being **63% vs. 32%** in the 5FU only arm. Recurrence rate also differed for the 2 groups, which were **34% and 69%** respectively. Lead investigator claims that ANP therapy may find application not only in the treatment of brain tumors as reported previously, but also in the more common colorectal cancer.

http://finance.yahoo.com/news/Metastatic-Colon-Cancer-In-a-bw-15355368.html?.v=1

12. Investigational Drug Vistonuridine Shows Promise as Treatment for 5FU Overexposure (May 28/09)

The emergency use of an investigational drug has yielded promising results in reducing the potentially fatal side effects of the widely used cancer chemotherapy 5-fluorouracil (5-FU), according to clinical data that was reported at the annual meeting of the American Society of Clinical Oncology (ASCO) in Orlando. The investigational drug, **vistonuridine**, was used to treat patients who had been accidentally overdosed with 5-FU and whose physicians had requested the drug for emergency use. Many undergo 5-FU therapy annually and that 1,300 die of 5-FU overexposure in the States, which can result from either overdoses or poor drug clearance. Currently, no antidote for 5-FU overexposure is approved by regulatory authorities. Vistonuridine is being developed by Wellstat Therapeutics Corporation. The presentation at ASCO reported on 17 cases of 5-FU overdose for which Wellstat supplied vistonuridine under emergency-use Investigational New Drug provisions of the Food and Drug Administration (FDA). Vistonuridine was flown or couriered to physicians immediately following their requests. The emergency treatment commenced as rapidly as possible after 5-FU overdose (within 8 to 96 hours), depending on the timing of the request to Wellstat and the location of the treatment site. All 17 of the vistonuridine-treated patients recovered, even though a fatal outcome for at least 13 of the patients would have been predicted by the dose and rate of 5-FU administration. Preclinical and clinical data indicate that earlier treatment with vistonuridine resulted in milder toxicity than did later treatment.

www.cancercompass.com/cancer-news/1,15784,00.htm

13. Tumor Shrinkage at 6 Weeks is a Predictor of Outcome in Chemorefractory Metastatic Colorectal Cancer Treated with Erbitux (May 29/09)

This study demonstrated that tumor shrinkage at 6 weeks is a strong predictor of time to progression (time before disease gets worse) and overall survival in chemorefractory (resistant to chemo used thus far) colorectal cancer patients treated with erbitux with or without irinotecan. This suggests that early

tumor shrinkage is the hallmark of efficacy of erbitux and reliably identifies those patients that are sensitive to the drug. According to the lead investigator, early tumor shrinkage can be used as a marker of efficacy in clinical practice, as such or in combination with others.

Piessevaux, H, et al., Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial). Annals of Oncology. Advance access published online on May 22, 2009. Annals of Oncology. Doi:10.1093/annonc/mdp011

14. Avastin & Early Stage Colon Cancer (Jun 1/09)

Researchers involved in an international multicenter study have reported that addition of Avastin (bevacizumab) to post-surgery chemotherapy **does not** improve disease-free survival among patients with early-stage colon cancer. The details of this Phase III clinical trial were presented at the 2009 annual meeting of the American Society of Clinical Oncology on May 31 in Orlando, Florida. The current results are from a Phase III clinical trial known as NSABP C-08. The study enrolled 2,710 patients with Stage II or Stage III colon cancer. After surgical removal of the primary cancer, patients were assigned to receive six months of chemotherapy alone with FOLFOX6 (oxaliplatin, leucovorin, 5-FU) or six months of chemotherapy plus Avastin followed by an additional six months of Avastin alone after chemotherapy had ended. After a median of three years' follow-up, **77.4%** of patients treated with chemotherapy plus Avastin were alive and free of disease compared with **75.5%** of patients treated with chemotherapy alone. The difference between study groups did not meet the criteria for statistical significance, suggesting that it could have occurred by chance alone. Interestingly, however, the Avastin group did experience better disease-free survival during the first year of the study (the year during which they received Avastin). In a prepared statement, one of the researchers noted: "Our overall conclusion is that Avastin was not effective as an adjuvant treatment for early-stage colon cancer (ie stage II and stage III), but the transient benefit we saw in patients who received Avastin illustrates that we have more to learn about how this reagent works, and we need to design more clinical trials to determine how it can be used most effectively."

Wolmark, N, et al., A phase III trial comparing Folfox6 to folfox 6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP protocol C-08. Presented at the 2009 annual meeting of the American Society of Clinical Oncology. May 29-June 2, 2009. Orlando, FL. Abstract LBA4

15. Vitamin K Boosts Cancer Drug Effects (Jun. 1/09)

A simple, non-toxic nutrient, vitamin K, may increase the effectiveness of a cancer treatment medication called sorafenib (Nexavar). This type of medication, known as a kinase inhibitor, has been used to treat kidney and liver cancer, and now is being studied as a possible treatment for other cancer types, including colon cancer. The study was conducted in the lab, using liver cancer cells, and demonstrated that at different dose levels of sorafenib and vitamin K, the combination of the drug and the vitamin together was more effective at killing cancer cells than either substance alone. The researchers concluded that vitamin K, which is a non-toxic nutrient, can decrease the amount of the drug sorafenib that is needed to cause cancer cell death. This research is exciting for a number of reasons, but one of the most important is that it points the way to the possibility of treating cancer more effectively, with fewer toxic side effects. One of the major problems with many current cancer treatment medications, including sorafenib, is that they can have serious, toxic side effects. In some people, the side effects can become severe enough that the dose of the drug being given must be reduced, to a potentially less-effective level, or the treatment must be discontinued altogether. By combining this particular medication, sorafenib, with vitamin K, doctors may be able to more effectively treat cancer with a lower, less toxic dose of the drug.

NB: Sorafenib is currently in clinical trials for the treatment of colorectal cancer.

2009 AACR Annual Meeting. Antibody Technologies. Carr, Brian, et al., Vitamin K1 enhances Sorafenib effects on HCC and induces apoptosis: a non toxic prevention strategy. Abstract # 5470.

16. Trabedersen Shows Promise in Treatment of Colorectal Cancer (Jun. 2/09)

Trabedersen (AP 12009), a first in-class investigational therapy for the treatment of aggressive tumors, showed a good safety and tolerability profile and encouraging survival data in patients with pancreatic carcinoma, malignant melanoma and **colorectal carcinoma**. Data from a Phase I/II study, announced at the American Society of Clinical Oncology (ASCO) 2009, will lead to further clinical studies. Currently an additional 24 patients with pancreatic carcinoma or malignant melanoma are being recruited to confirm the promising efficacy and safety results with trabedersen (Abstract 4619). In the trial, 33 patients with advanced pancreatic carcinoma, malignant melanoma or colorectal carcinoma were treated intravenously with trabedersen in two different treatment schedules. The primary objective of the study was to determine the maximum tolerated dose (MTD) and the secondary objectives were to investigate the safety and tolerability of trabedersen, its pharmacokinetics and antitumor activity. Very good safety and

tolerability of trabedersen was observed in the study, with moderate self-limiting thrombocytopenia (lowered platelet levels) the main adverse event seen. The MTD was established as 160 mg/m²/d in the first treatment schedule; MTD has not yet been reached in the second treatment schedule.

Oettle, Helmut, et al., ASCO. Abstract #4619. Interim Results of the Phase I/II Study of trabedersen (AP 12009) in Patients with pancreatic carcinoma, malignant melanoma or colorectal carcinoma.

17. Preemptive Skin Treatment Reduces Skin Toxicity Associated with Vectibix in Metastatic Colorectal Cancer Patients (Jun. 3/09)

Researchers affiliated with a U.S. multicenter trial have reported that skin treatment that is initiated prior to the start of treatment with Vectibix (panitumumab) reduces the incidence and severity of skin toxicity and improves quality of life in patients with metastatic colorectal cancer. The details of this study were presented at the 2009 annual meeting of the American Society of Clinical Oncology in Orlando, Florida, on June 1. The main side effects associated with Vectibix are skin reactions. These reactions can be mild to severe and often adversely affect a patient's quality of life. Researchers have been evaluating ways to minimize these side effects. The STEPP trial compared two different approaches aimed at minimizing skin reactions associated with treatment with Vectibix. This trial included 95 patients with metastatic colorectal cancer who were treated with Vectibix plus Camptosar (irinotecan) chemotherapy when they progressed after initial chemotherapy. Patients were randomly allocated to receive one of the following:

1) preemptive skin treatment, which started the day before beginning therapy and continued through the sixth week of therapy (48 patients), or

2) reactive treatment with multiple daily applications of skin moisturizer, sunscreen, topical steroids, and administration of doxycycline – an antibiotic, (remaining patients).

Of patients in the preemptive skin treatment group, **29%** experienced skin toxicity (grade 2 or higher) compared with **62%** of patients in the control group. Patients in the preemptive group had a **15%** incidence of grade 3 or greater skin toxicity compared with **28%** in the control group. Patients in the preemptive group reported experiencing a better quality of life during the study than those in the control group. There was a significant reduction in diarrhea, neutropenia (lowered white blood count), dehydration, and paronychia (inflammation of the nails) in the preemptive group compared with the control group. Overall response rate was 15% for patients in the preemptive group and 11% in the control group. As in other studies, responses were higher in patients with wild type KRAS and lower in those with KRAS mutations. Median progression free survival was 4.7 months for the preemptive group and 4.1 months for the control group. These researchers concluded that preemptive skin treatment helped reduce skin toxicity associated with EGFR treatment and improves quality of life in patients undergoing this treatment while still maintaining the anti-tumor efficacy of the treatment.

Mitchell EP, et al. Final STEPP results of prophylactic versus reactive skin toxicity (ST) treatment (tx) for panitumumab (pmab)-related ST in patients (pts) with metastatic colorectal cancer (mCRC). Presented at the 2009 annual meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL. Abstract CRA4027

18. Vorinostat in Combination with 5FU and Leucovorin (Jun. 3/09)

Roswell Park scientists in Buffalo are investigating a new combination of drugs for colorectal cancer patients who have become intolerant or resistant to standard therapies. Marwan Fakih presented the results of a phase I clinical study at the American Society of Clinical Oncology (ASCO) 2009 annual meeting, May 31, in Orlando, FL. Aggressive colorectal cancers can develop resistance to standard therapy of 5- fluorouracil (5-FU) and leucovorin, and progress. **Vorinostat** is a chemotherapy drug that modifies the structure of chromatin (DNA-protein complex) and therefore modifies the expression of various important genes that are associated in cancer growth. Vorinostat is of specific interest due to its ability to regulate the expression of the thymidylate synthase protein, which is associated with 5-FU resistance. Several laboratory studies have previously shown that the combination of vorinostat and 5-FU have greater anti-tumor activity than 5-FU alone. Researchers evaluated the effectiveness of 5-FU and vorinostat in 27 patients with solid tumors, including colorectal cancer, who had failed standard therapies. The investigators were able to escalate vorinostat safely up to 1700mg/day, three times a week, in combination with biweekly administration of 5-FU. Of the 24 colorectal cancer patients who were drug-resistant, one had a partial response lasting more than one year, and 12 patients had stable disease. The median time to disease progression was 4.4 months and the overall survival was 9.2 months. The results are encouraging, given that the overall survival of untreated advanced chemo-resistant colorectal cancer is 4.5 months. Researchers believe that vorinostat may overcome 5FU resistance. They are now conducting a phase II study of vorinostat plus 5FU in patients with refractory (chemo-resistant) colorectal cancer.

Fakih, Marwan, et al., A phase I Clinical trial of vorinostat in combination with sFULV2 in patients with refractory solid tumors. ASCO 2009. Abstract #4083.

19. Calcium/Magnesium Infusions are An Effective Strategy in Reducing Chemo-Induced Neuropathy (Jun. 4/09)

A randomized, double-blind, placebo-controlled phase III trial was conducted by the North Central Cancer Treatment Group wherein intravenous calcium and magnesium was administered to primary resected colorectal cancer patients receiving adjuvant folfox before and after oxaliplatin. Infusions of calcium and magnesium have been shown to protect against oxaliplatin-related chronic sensory neuropathy (toxicity that results in tingling and numbness of the finger and toes). The incidence of sensory neuropathy was significantly less frequent with mag/cal infusions vs. placebo. According to the patient reports, mag/cal infusions produced significant reductions in chronic, cumulative sensory neuropathy vs. placebo.

Grothey A., et al., Evaluation of the effect of intravenous calcium and magnesium (CaMg) on chronic and acute neurotoxicty associated with oxaliplatin: results from a placebo-controlled phase III trial. ASCO 2009, May 29-June 2, 2009; Orlando, Fl. Abstract 4025.

20. Managing Chemo-Related Nausea & Vomiting (Jun. 7/09)

Nausea and vomiting are among the most-dreaded side effects of cancer treatment, but research has given doctors an additional tool in the battle against chemotherapy-induced nausea and vomiting. This study focused on better ways to manage acute and delayed nausea and vomiting. Acute side effects are those that occur within the first 24 hours of receiving chemotherapy, whereas delayed effects are those that occur 24 to 120 hours (5 days) after chemotherapy. Delayed effects can be more difficult to manage. The study included 810 people from 77 cancer treatment facilities in 22 countries. Patients who were receiving highly emetogenic (likely to cause nausea and vomiting), cisplatin-based chemotherapy were treated with one of the following side effect management options:

- dexamethasone and ondansetron alone, standard anti-nausea and anti-vomiting medications
- dexamethasone and ondansetron plus one oral (by mouth) dose of an additional medication, **casopitant mesylate**
- dexamethasone and ondansetron plus **casopitant mesylate** both orally and for three days intravenously after chemotherapy

Study participants who received the extra medication, **casopitant mesylate,** either as a single dose or in multiple doses, had **less nausea and vomiting** than those who did not receive this drug. **66%** of people in the dexamethasone and ondansetron group had complete control of both acute and delayed nausea and vomiting vs. **86%** complete control in the single dose casopitant mesylate group and **80%** complete control in the multiple dose casopitant mesylate group. These medications are appropriate for use only with certain types of chemotherapy.

Grunberg, Steven, et al., Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomized, double blind, placebo-controlled trial. The Lancet Oncology. Vol 10, Issue 6; pp.549-558.

21. Imprime PGG in Kras-Mutated Colorectal Cancer Patients (Jun. 10/09)

Biothera has initiated a Phase II clinical trial in stage IV KRAS-mutated colorectal cancer patients with its investigational drug **Imprime PGG** in combination with Erbitux (cetuximab). Published research demonstrates that colorectal cancers with mutated KRAS genes do not respond to anti-EGFR monoclonal antibodies such as Erbitux. However, researchers believe that Imprime PGG uses the body's own immune system by engaging a type of white blood cell called the neutrophil to fight cancer cells that are coated with antibodies like Erbitux. Such a strategy might be effective against tumors regardless of whether KRAS is mutated or not. Preclinical studies indicate that Imprime PGG in combination with Erbitux can reduce tumor growth. According to the lead researcher, about 35-40% of all colorectal cancers have a mutation in the KRAS gene. Erbitux and related antibodies are ineffective against these KRAS-mutated cells. While Erbitux doesn't kill cancer cells that have mutated KRAS, it can bind to the tumor cells and activate the binding of another protein in the immune system called complement to the tumor cell. When neutrophils primed with Imprime PGG bind to the "fixed" complement on the tumor cell, the neutrophils can attack the cancer cell and promote death. Imprime PGG is being developed as combination treatment for a wide range of cancers, including **colorectal** and lung cancer. In this trial design, since drugs like Erbitux alone can't work in a KRAS-mutated tumor, if patients' tumors are observed to shrink, then there will be a high degree of confidence that it is the presence of the investigational drug that is making that happen. The open-label, 56-patient KRAS-mutated colorectal cancer study is being conducted at three U.S. locations (New York, Minneapolis and Dallas). All subjects will receive Imprime PGG at 4 mg/kg weekly plus standard doses of Erbitux. Based

on the results of the first clinical trial in second- and third-line metastatic colorectal cancer patients, the prospect that Imprime PGG in combination with monoclonal anti-EGFR therapies might provide hope to patients with KRAS-mutated tumors is exciting. This KRAS-mutated colorectal trial has the potential to become a pivotal trial and may lead to a fast-track application to the FDA. To access a video which explains the process of how Imprime PGG attracts immune system cells (neutrophils) to cancer cells where they then destroy the cancer, click on the following link:
http://www.biotherapharma.com/popups/BiotheraAnimation-Injectable.html

www.medicalnewstoday.com/articles/153574.php

22. Adding Oxaliplatin to Chemoradiotherapy Before Rectal Surgery Does Not Improve Surgical Response (Jun. 13/09)

An Italian trial (STAR study) found that adding oxaliplatin to chemoradiotherapy before rectal surgery did nothing to improve the rate of complete responses found at surgery. There was also no decrease in the number of patients who needed a permanent colostomy. Serious diarrhea was significantly worse in the oxaliplatin arm. However, there was an unexpected occurrence. There were more distant metastases found at the time of surgery among patients who did not receive oxaliplatin (16 patients with spread to lungs, liver, or peritoneal surfaces vs. only 2 who received oxaliplatin prior to surgery). The survival data will be forthcoming in respect of this trial.

Aschele, C., et al., Preoperative fluorouracil (FU)-based Chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial. J Clin Oncology. Vol. 27: 18s, 2009 (suppl; abstract CRA4008) ASCO 2009.

23. Microsatellite Instability and Stage III Colon Cancer – Possible Benefit from Irinotecan (Jun. 13/09)

About 15% of people with stage III colon cancer may have fewer recurrences and better survival when they are treated with irinotecan. Although all stage III colon cancers don't have an additional benefit when irinotecan is added to bolus 5-FU and leucovorin in a treatment called IFL, this smaller group of 15% does. About 15% of colon cancers develop when damaged DNA is not repaired and mutated cells grow into malignant tumors. So-called ***deficient mismatch repair (dMMR)*** **tumors** have features different from most colorectal cancer, including a <u>better</u> prognosis. They also have a very <u>poor response to 5-FU-based chemotherapy</u>. However, researchers studying tumor tissue from patients enrolled in a clinical trial comparing 5-FU and leucovorin alone to 5-FU, leucovorin, and irinotecan found that those with **deficient mismatch repair tumors** who received irinotecan had **better disease-free survival** and overall survival at five years than patients whose mismatch repair genes were working (intact). Those with dMMR in the 5-FU-only arm of the trial had no similar benefit. Deficient mismatch repair can be identified by measuring mutated **<u>microsatellites</u> — short lengths of DNA that are abnormally shorter or longer because they were not caught and corrected during cell division (see diagram below).** This is known as **<u>microsatellite instability</u>** or MSI. dMMR can also be diagnosed by looking for missing mismatch repair gene expression in tumor tissue. To find out if there was any benefit for irinotecan in deficient mismatch repair tumors, researchers tested tissue saved after surgery for both MSI and loss of MLH1 and MSH2 gene expression from patients enrolled in the CALGB-89803 clinical trial. The trial randomly assigned stage III colon cancer patients after surgery to chemotherapy of intravenous 5-FU plus intravenous leucovorin (FU/LV) or the same 5-FU and leucovorin treatment plus irinotecan (IFL). Chemotherapy was given every week. For all of the nearly 1,300 people enrolled in the trial, there was no significant difference in overall survival after 5 years (70% for IFL and 72% for FU/LV). There was a significant increase in toxic side effects in the IFL arm and some unexpected deaths. *However, when tumors were analyzed for deficient mismatch repair status (dMMR), as evidenced by high microsatellite instability (MSI-H) compared to intact mismatch repair (iMMR) or low or stable microsatellite stability (MSI-L/S),* ***adding irinotecan did make a difference in disease free survival and overall survival five years after surgery:***

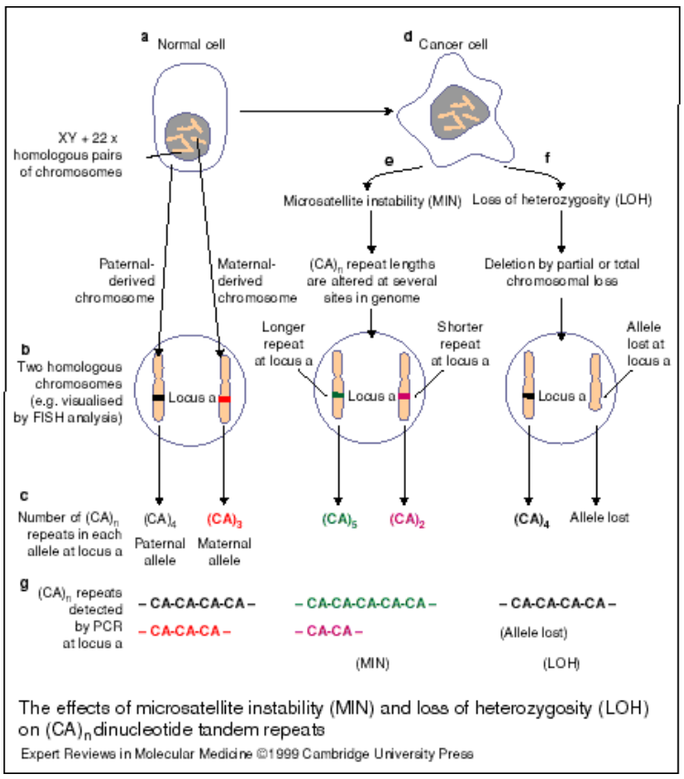
Five year disease free survival

- All patients: 61%
- FU/LV and MMR-D (MSI-high): 57%
- FU/LV and MMR-I (MSI low or stable): 51% (no significant difference)
- IFL and MMR-I: 59%
- IFL and MMR-D: **76%** (significant difference in this group)

Overall survival at five years

- All patients: 67%
- FU/LV MMR-D: 67%
- FU/LV MMR-I: 72%
- IFL MMR-I: 70%
- IFL MMR-D: **78%** (significant difference in this group of patients)

Some, but not all, dMMR tumors are caused by inherited genetic mutations in mismatch repair genes. Since colon cancer caused by deficient mismatch repair does not benefit from 5-FU chemotherapy, it is becoming common to test for MSI in tissue removed during surgery before prescribing chemotherapy.



The effects of microsatellite instability (MIN) and loss of heterozygosity (LOH) on $(CA)_n$ dinucleotide tandem repeats

Source:
www.google.com/imgres?imgurl=http://journals.cambridge.org/fulltext_content/ERM/ERM1_08/S1462399499000526sup014.gif&imgrefurl=http://journals.cambridge.org/fulltext_content/ERM/ERM1_08/S1462399499000526sup010.htm&h=500&w=441&sz=15&tbnid=VxpQ3oGJhPQ5uM:&tbnh=130&tbnw=115&prev=/images%3Fq%3Dmicrosatellite%2Binstability%2Bpicture&hl=en&usg=__yPHBtx_nUHiJhlAYxvxxIq29L_k=&ei=rYY6SsT8KY60Nbn74K4F&sa=X&oi=image_result&resnum=4&ct=image

Bertagnolli, Monica, et al., Microsatellite Instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil, and leucovorin in stage III colon cancer: cancer and leukemia group B protocol 89803. J of Clin Oncology: vol 27, #11, 2009, pp.1814-1821.

24. Comparing Folfox to Folfiri in Patients Previously Treated with FU-Therapy (Jun. 15/09)

This phase III trial sought to determine whether overall survival of FU-resistant patients was noninferior when treated with second line infusional FU, leucovorin, and oxaliplatin (folfox4) vs. irinotecan (folfiri). Patients who experienced treatment failure with one prior FU based therapy and had not received prior irinotecan or oxaliplatin, either for metastatic disease or within 6 months of adjuvant FU therapy, were randomly assigned to either arm A (folfiri) or arm B (folfox). The results confirmed that in patients who experienced treatment failure with front-line FU therapy, overall survival does not significantly differ whether second-line therapy begins with folfiri or folfox. Folfox, however, produced higher response rates and longer time to progression (time before disease got worse). Both arms had notable overall survival in patients who experienced treatment failure with first line FU therapy. Irinotecan therapy was associated with more grade 3 nausea, vomiting, diarrhea and neutropenia (lowered white blood counts); whereas folfox was associated with more neutropenia and paresthesias (tingling of fingers and toes).

Kim, George P, et al., Phase III Noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. J of Clinical Oncology, Vol. 27, #17: June 10, 2009: pp. 2848-2854.

SURGICAL

25. Abdominosacral Amputation for Low Rectal Cancers (May 26/09)

Abdominoperineal resection for rectal cancer is related to a high frequency of local recurrences, risk of inadvertent bowel perforation, and disease-positive tumor margin. An alternative technique to this procedure, however, is the **abdominosacral amputation of the rectum (ASAR).** The aim of this study was to report on the technique and share the experience of ASAR on the 210 operated patients. At the beginning, ASAR follows the rules of total mesorectal excision. Towards the end, the patient is positioned in a prone jackknife position and the coccyx (tailbone) and the last sacral vertebra (if necessary) are removed, enabling a sharp and directly visualized resection of the tumor and other structures critical to local recurrence for low rectal cancers. The results demonstrated that ASAR had a low risk of bowel perforation, circumferential resection margin involvement and local wound complications. The local recurrence rate was lower and survival better than with conventional abdominoperineal resection.

Bebenek, Marek, Abdominosacral Amputation of the Rectum for low rectal cancers: ten years of experience. Annals of Surgical Oncology. Published online May 19, 2009. DOI:10.1245/s10434-009-0517-2

26. Surgical Removal of Primary Unnecessary for Most Metastatic Colorectal Cancer Patients (Jun. 209)

Researchers from Memorial Sloan-Kettering have reported that patients with newly diagnosed metastatic colorectal cancer do not need to undergo surgical removal of their primary tumor unless the tumor is causing complications. Historically, standard treatment for metastatic colorectal cancer was removal of the primary tumor at the time of diagnosis. This was not to extend survival, but to prevent future complications that could be caused by the tumor. However, many new chemotherapy drugs have proven effective in the treatment of metastatic colorectal cancer, and physicians have begun to speculate that surgical removal of the primary tumor is unnecessary and may carry more risk than benefit. Furthermore, immediate surgery often results in the delayed use of chemotherapy. Researchers involved in this study conducted a retrospective analysis of 233 consecutive patients diagnosed with metastatic colorectal cancer between 2000 and 2006 whose symptoms did not warrant immediate surgery. The patients were treated with one of three triple-drug regimens FOLFOX, IFL and FOLFIRI with or without the addition of the targeted agent Avastin. 93% of patients in this study never required surgery. 7% required emergency surgery for obstruction or perforation. 4% of patients required non-operative intervention such as a stent or radiation therapy. Thus, 89% of patients did not require any intervention. 20% of patients ultimately had elective colon resection at the time of surgical removal of metastatic lesions, and eight had colon resection at the time of hepatic artery infusion pump placement. The results indicated that the majority of patients never developed complications that necessitated surgical removal of their tumor. The researchers concluded that most patients with metastatic colorectal cancer who receive immediate treatment with chemotherapy never require surgical removal of their tumor. They suggest that chemotherapy should be the standard of care for patients with metastatic colorectal cancer who do not have obstructed or bleeding colorectal tumors.

Poultsides GA, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. Presented at the 2009 annual meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL. Abstract CRA4030.

27. Complete Resection of Large Nonpedunculated (Flat) Colon Polyps Using Endoscopic Submucosal Dissection (Jun. 1/09)

Endoscopic Submucosal Dissection (ESD) has emerged as one of the techniques to successfully resect large colonic polyps **en bloc** (in one large piece). Complete resection prevents the patient from going through Transabdominal colonic resection (conventional surgery). This study sought to evaluate the proportion of successful en-block and complete cure en-bloc resection of large colonic polyps by ESD. Studies that used ESD technique to resect large colonic polyps were selected to be part of this study and there were 389. Successful en-bloc resection was defined as resection of the polyp in one piece. Successful complete cure en-bloc resection was defined as one piece with disease free margins. The results of the respective studies demonstrated that the complete cure en-bloc resection was **75.39%**. Researchers concluded that ESD should be considered the best minimally invasive endoscopic technique in the treatment of large (> 2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. ESD offers an important alternative to surgery in the therapy of large sessile and flat polyps.

Puli, Srinivas, et al., Successful Complete Cure En-Bloc Resection of large Nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. Annals of Surgical Oncology: Online Edition. DOI: 10.1245/s10434-009-0520-7. May 29, 2009.

28. Surgery for Right Sided Colon Cancer That Has Spread to the Duodenum (Jun. 8/09)

Cancer of the colon with spread into adjacent structures or organs is not an infrequent event. Right side colon cancer invasion of the duodenum (first part of the small intestine) or pancreas is rare. The rate of duodenal involvement is reported to be 0 - 12 %. This lower rate is likely due to right colon cancers being diagnosed earlier (as a consequence of symptoms of obstruction and bleeding), before they can become large masses that have the potential to invade retroperitoneal organs such as the duodenum and pancreas. Although right-sided colon cancer involving the duodenum and pancreas is infrequent, this condition represents a challenge for the surgeon because extended radical resection is controversial. However, in the past decade, many reports have shown that en bloc resection (removal of tumour in one piece) of the tumor and all adjacent structures is the optimal treatment for these patients. Patients who undergo en bloc resections of their cancer and all adjacent structures (40-61%) have a higher 5-year survival rate compared with those treated via separation of affected organs (23 %). Any attempt to separate the cancer from affected organs may cause the cancer cells to seed into the abdomen, increasing the risk of recurrence. According researchers, early local recurrence has been reported in 70 to 100% of the patients treated with a non en-bloc resection. Therefore, en bloc resection of the tumor with affected organs is being advocated. In this study, 12 patients underwent en bloc resection and eight underwent palliative surgery, with no deaths. There was one 10-year survivor, four 5-year survivors, and three 3-year survivors among the 12 patients treated via en bloc resection, whereas all eight patients

treated via palliative resection died within 18 months. Researchers concluded that duodenal invasion by a right-sided colon carcinoma does not necessarily represent incurable disease. If carefully applied based on the extent of duodenal invasion, active surgical management is very useful for improving patient prognosis without increasing the risks associated with surgery. Researchers maintained that invasion of the duodenum by right-side colon carcinoma is often a challenge for the surgeon, but it is not an absolutely incurable disease. A surgical procedure carefully adjusted to the extent of carcinoma invasion can offer patients the chance for long-term survival.

Lianwen, Y, et al., Surgical treatment for right colon cancer directly invading the duodenum. The American Surgeon. 2009 May; 75(5): 385-388

29. Surgically Addressing Liver & Peritoneal Mets (Jun. 9/09)

Patients with colorectal cancer that has spread both to their livers (*hepatic metastases)* and to their abdominal cavities (**peritoneal** *carcinomatosis)* can be helped with ***combination surgery that removes both***. In the past, cytoreductive surgery with heated intraperitoneal chemotherapy (IPHC or HIPEC) has been limited to patients who didn't have mets in their liver. However, a study of 142 patients, included 14 with liver mets, who had cytoreductive surgery for their peritoneal carcinomatosis showed no difference in overall survival. Median survival for the patients with liver mets was 23 months. At two and four years, 43.3% and 14.4% of patients with liver mets were still alive compared to **36.8% and 17.4%** of those without spread to their livers. Most patients had a single small liver tumor. Dr. Oliver Varban and the surgeons at Wake Forest University in North Carolina are accomplishing much in the way of surgical removal of both hepatic and peritoneal mets.

Those patients wishing to explore candidacy for or pursue combination surgery for liver and peritoneal metastases, may contact Dr. Perry Shen at pshen@wfubmc.edu , Department of General Surgery. Surgical Oncology Section, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC, 27157. Fax: 336 713 6959

Varban, Oliver, et al., Outcomes associated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in colorectal cancer patients with peritoneal surface disease and hepatic metastases. J of Cancer. Published online June 4, 2009.

30. Factors Associated with Local Recurrence After Neoadjuvant (Preoperative) Chemoradiation with Total Mesorectal Excision For Rectal Cancer (Jun. 9/09)

This study investigated the risk factors associated with local recurrence in patients with locally advanced rectal cancer who received preoperative chemoradiotherapy (chemo plus radiation therapy) in combination with total mesorectal excision (TME – surgical removal of their primary rectal tumor). 26 patients who developed local recurrence were compared with 119 recurrence free patients during the follow up. It was found that patients with the following should be regarded as a high risk group:

- **circumferential margin involvement** (the presence of tumour within 1 mm of the circumferential margin of the primary tumour)
- presence of **lymphovasuclar or perineural invasion,** (presence of the invasion of the cancer cells into the blood vessels or lymphatic channels and the invasion of cancer cells into one or more nerves). and
- positive **nodal disease** should be regarded as a high risk group.
- It was also determined that **lymph node retrieval (< 12 nodes)** in patients with node-negative disease was a risk factor for local recurrence.

Kim, Nam-Kyu, et al., Factors associated with local recurrence after neoadjuvant Chemoradiation with total mesorectal excision for rectal cancer. World J of Surgery. Published online. June 4, 2009. DOI: 10.1007/s00268-009-0077-4

31. Study Evaluating the Treatment of Synchronous Liver Mets & Colorectal Primary (Jun. 12/09)

Patients who have their liver mets discovered at the same time as their colorectal primary are typically treated with initial colorectal primary resection followed by arbitrary and prolonged courses of chemo. A partial hepatectomy (liver resection) is considered only for patients without interval disease progression. This study described the rationale for this treatment approach and the recent developments suggesting that this management of the disease **should be reconsidered.** Because asymptomatic (demonstrating no symptoms) colorectal cancer often does not lead to complications and given the potential benefit of chemotherapy in downsizing unresectable to operable liver disease, most patients with asymptomatic primary tumors and unresectable synchronous colorectal liver mets should be first treated with chemotherapy according to these researchers from Duke University Medical Center. They further maintain that initial liver resection should be considered for resectable synchronous colorectal liver mets (surgical removal of both primary and liver mets). Survival benefits from neoadjuvant chemotherapy (chemo given before liver surgery) have not been established. Several reports demonstrate morbidity after hepatic resection from extended durations of irinotecan- and/or oxaliplatin-based prehepatectomy chemotherapy (chemo given before liver surgery). Finally, the researchers maintain that several studies suggest that simultaneous colorectal and minor hepatic resections can be performed safely with benefits in total morbidity when compared with traditional staged procedures. Researchers concluded that the traditional treatment standard centering on the usefulness of prehepatectomy chemotherapy for

resectable synchronous colorectal liver mets should be reconsidered. The researchers are emphasizing the need for prospective randomized controlled trials evaluating the optimal timing of hepatectomy relative to chemotherapy.

Reddy, Srinevas, et al., Synchronous Colorectal Liver Metastases: is it time to reconsider traditional paradigms of management? Annals of Surgical Oncology. June 9, 2009. Published online. DOI: 10.1245/s10434-009-0372-1.

32. Response to Neoadjuvant Chemo in Preparation for Liver Mets Surgery (Jun. 17/09)

This study investigated the relation between response to neoadjuvant chemotherapy (chemo given before surgery) and overall survival in patients with colorectal liver metastases. Patients with synchronous colorectal liver mets whose disease progresses while receiving neoadjuvant chemotherapy or who do not receive neoadjuvant chemotherapy appear to experience worse survival than patients whose disease responds to neoadjuvant chemotherapy. This study sought to either verify this concept or refute it. 111 patients with synchronous colorectal cancer liver metastases received neoadjuvant chemotherapy before hepatic resection. The disease of all 111 patients was deemed resectable, and patients underwent liver resection with the intent to cure (curative intent). The median overall survival after liver resection was 62 months, with a median follow-up of 63 months. Median overall survival was similar between the three study groups based on the response to neoadjuvant chemotherapy (complete or partial response, 58 months; stable disease, 65 months; and disease progression, 61 months;). The following factors were all associated with improved survival:

- Carcinoembryonic antigen (CEA) level after liver resection of <5 ng/dL (US level) (Cdn level <4),
- size of metastatic lesion of < 5 cm,
- lymph node-negative primary colorectal tumor, and
- disease-negative margins

Patients in the disease progression group had more positive margins and metastases >5 cm in size than patients in the complete or partial response group and the stable disease group. Patients whose tumor progressed but who received postoperative hepatic arterial infusion (infusing chemo directly into the liver) had a trend toward improved survival compared with those who did not receive hepatic arterial infusion (70% vs. 50% overall survival at 3 years). **Researchers concluded that patients who had tumors shrink in response to chemo given before they had liver surgery for colorectal cancer that had spread to their livers had no better long term survival than patients whose cancer remained the same or even got worse, even after controlling for margins, stage of primary tumor, and postoperative carcinoembryonic antigen level.**

Gallagher, David J, et al., Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Annals of Surgical Oncology. Vol. 16, No. 7, July 2009. Published online.

RADIATION/INTERVENTIONAL RADIOLOGY

33. Early Prediction of Response to First-Line Chemo by PET in Colorectal Cancer (May 22/09)

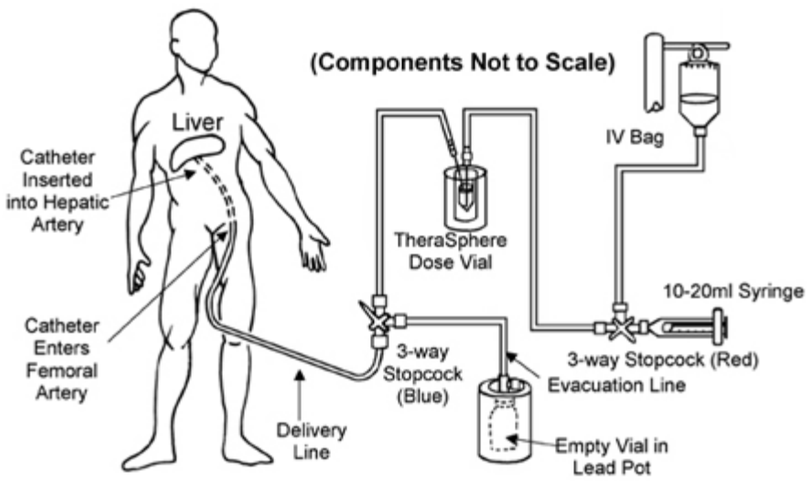
Trying to predict whether or not chemotherapy was working as soon as possible, Swedish doctors compared FDG-PET scanning before beginning chemo and after two treatments. Then they looked at CT scans after 4 and 8 treatments to see if early PET scans could predict changes in tumor size. They found that the scans did show which patients would respond to treatments with tumor shrinkage. Patients who responded had greater reduction in metabolic readings on PET scans than did patients whose tumors didn't get smaller. But changes in PET values did not predict benefits in either the time until cancer got worse (*progression-free interval)* or overall survival. Patients who responded to chemotherapy with tumor shrinkage had the lowest standardized uptake values (SUVs - the ratio of metabolic activity in tissue per milliliter to the activity in the injected dose per patient body weight) on PET scans before chemotherapy began. Non-responders showed higher metabolism within tumors on PET before chemotherapy. Researchers concluded that "although metabolic response assessed by FDG-PET reflects radiological tumor volume changes, the sensitivity and specificity are too low to support the routine use of PET in metastatic colorectal cancer. Furthermore, PET failed to reflect long-term outcome and can, thus, not be used as surrogate end point for hard endpoint benefit."

Bystrom, p, et al., Early prediction of response to first-line chemotherapy by sequential [F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with advanced colorectal cancer. Annals of Oncology. Vol. 20, No. 6: pp.1057-1061.

34. Radioactive Resin Microspheres Shows Delay in Disease Progression in Patients with Colorectal Cancer Liver Mets who Have Exhausted Chemo (Jun. 1/09)

The time to progression of disease in patients with colorectal cancer liver metastases who have exhausted all chemotherapy options can be more than doubled through the use of radioactive resin microspheres, according to the results of this study which were presented at this year's ASCO. The phase III study compared the use of 5-fluorouracil (5FU) alone to 5FU plus 90Y (yttrium 90) resin microspheres (SIR-Spheres – radiation-containing beads) on patients in Belgium. Patients with colorectal cancer liver metastases who are resistant or intolerant of chemotherapy should be considered

for salvage therapy using 90Y resin microspheres combined with 5FU-based chemotherapy, according to the lead investigator. The addition of 90Y resin microspheres to systemic 5FU significantly prolonged the time to progression compared with 5FU alone, more than doubling the interval before disease recurrence in the liver or anywhere in the body, and was well tolerated by patients who had already received many previous lines of chemotherapy. The median time to progression of liver disease – which was the primary endpoint of the study - increased from 2.1 months with 5FU alone to 5.5 months with 5FU plus 90Y resin microspheres while the median time to progression of disease anywhere in the body was 2.1 vs. 4.6 months, respectively. The proportion of patients with disease control following the combination treatment was also increased significantly from **35% to 85%**, respectively with one patient (5%) receiving 5FU plus 90Y resin microspheres having a sufficiently large reduction in tumor size to permit potentially curative surgical resection of the remaining disease in their liver. All 44 patients in the study had colorectal cancer restricted to the liver, a median age of 62 and had failed or could not tolerate multiple prior lines of standard-of-care chemotherapy comprising 5FU, oxaliplatin, irinotecan and available biological agents. Treatment with 5FU plus 90Y resin microspheres was well tolerated, with significantly more patients experiencing a serious adverse event in the 5FU-only control arm (4% vs. 35%, respectively). The encouraging results of this randomized trial confirm the findings from single-arm and retrospective studies of 90Y resin microspheres that have reported median overall survivals in the order of 10 to 13 months when used alone as salvage therapy for patients with liver-dominant metastatic colorectal cancer who have exhausted all chemotherapy options.



Microspheres, also known as Theraspheres, are delivered to the liver via a catheter placed into the femoral artery and guided by fluoroscopy to the hepatic artery. Using this technique, the physician directs the catheter into the diseased lobe of the liver by following the appropriate branch of the hepatic artery. Once the catheter is properly positioned, the physician infuses the radioactive beads, which become localized preferentially in the tumor. Precise lobar administration prevents the inadvertent flow of microspheres into the gastrointestinal tract. Source: http://www.nordion.com/therasphere/physicians-faqs.asp

Van den Eynde, M, et al., Prospective randomized study comparing intra-arterial injection of yttrium-90 resin microspheres with protracted IV 5FU continuous infusion vs. IV 5FU continuous infusion alone for patients with liver-limited metastatic colorectal cancer refractory to standard chemotherapy. 45th ASCO Annual Meeting Proceedings. J of Clinical Oncology, 2009; 27 (Suppl 7s): Abstract 4096.

35. PET Predicts Early Metastatic Colorectal Cancer Response to Chemo – Another Study (Jun. 10/09)

FDG-PET continues to gain ground as a potential go-to modality for assessing post-chemotherapy response, Belgian researchers reported at the 2009 American Society of Clinical Oncology meeting. According to the lead investigator, the clinical experience suggests FDG-PET can find with near 100% certainty after a single course of chemotherapy, if a patient with metastatic colorectal cancer and is not responding positively to treatment. The results show that if tumor metabolism does not respond after 14 days, the patient is not likely to experience tumor shrinkage two or three months later on. Finding this out early on in treatment can help patients avoid unnecessary side effects and also allows them to try another type of therapy sooner, if possible, to optimize results.

Researchers wished to determine sooner than with the classic CT scan or MRI whether the patient would be likely to benefit or not from the chemotherapy regimen they were accessing. Researchers hypothesized that metabolic changes seen by comparing quantitative FDG-PET scans acquired before and two weeks after the first dose of chemotherapy would be predictive of a response for patients with advanced colorectal cancer. The prospective study compared early metabolic changes as measured by FDG-PET with morphological changes assessed by standard CT. Researchers presented interim results in 28 patients (median age, 65.9 years) with a total of 88 lesions, which were available for comparison. The mean number of lesions per patient was three, with a range of one to eight. The lesions were all visible and individualized on both analyses and measured at least 15 mm diameter on baseline CT. The chemotherapy regimens consisted of FOLFOX in 18 patients, FOLFIRI in 9 patients and Xeloda in 1 patient. 19 patients were receiving first-line chemotherapy, and 9 were receiving second-line treatment. An early metabolic response was defined as a 15% or greater decrease of the standardized FDG uptake

(SUV_{max}) on day 14 after the first chemotherapy dose. A patient was deemed to have overall metabolic responsive disease if most or all of the lesions observed on the baseline PET showed a metabolic response, without any progressive lesion. The authors noted that early metabolic response after one course of chemotherapy correlated with standard CT performed six to eight weeks after the initiation of chemotherapy. A positive response was observed in 6 of 14 (43%) patients experiencing a metabolic response based on PET scans and in 0 of 14 (0%) metabolically non-responding patients. **FDG-PET seems able to identify advanced colorectal cancer that is unlikely to show a response to chemotherapy, and it does so with a predictive value of 100%, according to lead investigator Hendlisz.**

www.diagnosticimaging.com/imaging-trends-advances/practical-ct/article/113619/1421467

36. Improved Selection of Patients for Hepatic Surgery of CRC Mets Using PET (Jun. 18/09)

With the increasing possibilities for surgical treatment of colorectal liver metastases, careful selection of patients who may benefit from surgical treatment becomes very important. The addition of PET may significantly improve conventional staging by CT. Up to now, definitive evidence that the addition of PET to conventional staging leads to superior clinical results and improved clinical management in these patients has been lacking. In this randomized controlled trial in patients with colorectal liver metastases, researchers investigated whether the addition of PET is beneficial and reduces the number of futile surgeries. A total of 150 patients with colorectal liver metastases selected for surgical treatment by imaging with CT were randomly assigned to CT only or CT plus PET. Patients were followed up for at least 3 years. The primary outcome that was to be measured (endpoint) was futile liver surgeries, defined as any laparotomy (surgery for liver mets) that did not result in complete tumor treatment, that revealed benign disease, or that did not result in a disease-free survival period longer than 6 months. The number of futile surgeries was 34 (45%) in the control arm without PET and 21 (28%) in the experimental arm with PET. The number of futile surgeries was **reduced from 45% to 28%;** thus, the addition of PET to the work-up for surgical resection of colorectal liver metastases prevents unnecessary surgery in 1 of 6 patients.

Ruers, TJM, et al., Improved Selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: a randomized study. The J of Nuclear Medicine. Published online June 12, 2009. doi: 10.2967/jnumed.109.063040.

SCREENING

37. Sigmoidoscopy Not Reducing Colorectal Cancer (Jun. 1/09)

A large randomized trial showed that flexible sigmoidoscopy screening failed to significantly reduce colorectal cancer incidence and mortality. The trial, called NORCCAP (NORwegian Colorectal CAncer Prevention), is the first large randomized study to report on the efficacy of sigmoidoscopy-based screening. NORCCAP randomized nearly 55,000 apparently healthy individuals, 50 to 64 years old, to screening with flexible sigmoidoscopy, accompanied in some patients by fecal occult blood testing, or to usual care. Assignments were made at a 1:3 ratio to screening versus control. The control participants were not offered screening and did not otherwise interact with study personnel. Participants in the screening group with positive findings then underwent full colonoscopy and polypectomy (removal of polyps). The primary endpoints (objectives) of the ongoing study are incidence and mortality of colorectal cancer at 5, 10, and 15 years. The incidence of colorectal cancer was 134.5 cases per 100,000 in the screened group and 131.9 cases per 100,000 in the unscreened group. No statistically significant difference was found in the 7-year incidence of colorectal cancer between the screening and control groups. According to the lead investigator, it appears that 7 years is too early to say whether this type of screening reduces deaths from colorectal cancer. He maintains that the cancer-reducing effect of screening may be lower and will certainly occur later than anticipated. The researchers offered 2 possible explanations for the unexpectedly small effect of flexible sigmoidoscopy screening. First, "...either the method is not effective in reducing colorectal cancer..." or second, "...the lag period for the development of cancer from precursor lesions is considerably longer than is commonly assumed." But he also noted that the data from this and other studies of sigmoidoscopy suggest the longer-term benefit is mainly **in preventing cancers occurring within range of the sigmoidoscope, which only visualizes the final one-third of the colon.** In the U.S., the use of sigmoidoscopy in place of full colonoscopy is controversial for this reason. (See: ***Sigmoidoscopy for Women Has Biological Deficiencies*** (http://www.medpagetoday.com/Gastroenterology/ColonCancer/1068) and ***Mortality from Right-Side Colon Cancer Not Lowered by Colonoscopy*** (http://www.medpagetoday.com/Gastroenterology/ColonCancer/12169).

Hoff, G, et al., Risk of colorectal cancer seven years after flexible sigmoidoscopy screening randomized controlled trial. BMJ 2009; DOI: 10.1136/bmj.b1846.

OTHER

38. Oncotype DX Predicts Return of Colon Cancer (May 15/09)

According to the results of a study that were presented at the 2009 ASCO conference, the Oncotype DX colon cancer test estimates the risk of cancer recurrence among patients with stage II colon cancer. This test may eventually help guide colon cancer treatment decisions. Gene expression profiling explores the patterns of genes that are active in tumor cells. Studies suggest that gene expression may provide important information about prognosis or likely response to treatment in several types of cancer. The test evaluates the activity of 21 genes from a sample of the patient's cancer to determine the patient's Recurrence Score. The Recurrence Score ranges from 0 to 100, with a higher score indicating a greater risk of recurrence. Research now indicates that this test may provide important information for patients with Stage II colon cancer. Many patients with this stage of disease have good outcomes with surgery alone, and routine adjuvant (post-surgery) chemotherapy is not currently recommended for Stage II colon cancer. Chemotherapy may, however, be considered for Stage II patients with a higher risk of cancer recurrence. Use of the Oncotype DX colon cancer test may allow for more accurate identification of these higher-risk patients. This study included over 1800 patients with stage II colon cancer. After development, the test was further tested in more than 1400 additional patients. The results indicated that the 18 gene Oncotype DX colon cancer test predicted risk of recurrence after surgery for Stage II colon cancer and provided information beyond that of standard markers of risk. However, it could not prove that 6 genes could predict who would benefit from treatment with 5FU and leucovorin over surgery alone. The lead researcher, Dr. David Kerr discusses the importance of combining recurrence risk scores with information about tumor stage and MSI (microsatellite instability status – discussed above) in making decisions about chemotherapy for stage II patients. For the authors did note that adjuvant (post surgical) chemotherapy was definitely of benefit to patients. Genomic Health, the company that developed both the Oncotype DX breast cancer test and the Oncotype DX colon cancer test, plans to make the Oncotype DX colon cancer test available in early 2010.

2009 ASCO Annual Meeting. Kerr, D, et al., A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study. Abstract #4000.

39. A New Marker Found For Colorectal Cancer (May 22/09)

Colorectal cancer is thought to result from a combination of environmental factors, diet, lifestyle, chronic inflammation and accumulation of specific genetic alterations. The development of colorectal cancer involves multi-genes and multi-steps. TSPAN1 is a newly identified gene located at chromosome 1 p34.1. It encodes a 241 amino acid-long protein. TSPAN1 was reported as a tumor-related gene recently. This latest study investigated the association between TSPAN1 and human colorectal adenocarcinoma and the results showed that there were significant differences between colorectal adenocarcinoma and normal control tissue. Protein expression in colorectal cancerous tissue was significantly linked with the histological grade, cell expression, lymph nodal metastasis and TNM staging of the disease. Patients with TSPAN1 protein over expression had a significantly shorter survival period than that in patients with TSPAN1 protein negative or weak expression, respectively. Furthermore, researchers concluded that TSPAN1 protein expression demonstrated an independent prognostic factor for human colorectal cancers. The lead investigator maintains that TSPAN1 expression in tissues would be a useful tool to evaluate the prognosis of patients with colorectal cancer.

Chen, L., et al., TSPAN1 protein expression: A significant prognostic indicator for patients with colorectal adenocarcinoma. World J Gastroenterology 2009; 15(18): pp. 2270-2276.

40. Comparing Molecular Markers for Stage II and Stage III Colon Cancer (Jun. 17/09)

Prognostic molecular markers tell us how likely cancer is to recur or patients to survive regardless of treatment. This study indicated that prognostic molecular markers were quite different between stage II and stage III colon cancer. 8 different markers in tumor tissue from the PETACC-3 study were analyzed. The different markers that were used were:

- P53 gene
- SMAD4 gene
- Thymidylate synthetase (TS)
- hTERT
- Kras and Braf gene mutations
- Microsatellite Instability (MSI)
- 18qLOH

The conclusions were as follows:

- While **MSI** or microsatellite instability was a strong marker of good prognosis in stage II, it lost its value as a prognostic marker completely in **stage III**.
- **P53** and the **SMAD4 genes** had prognostic value for **stage III** but not for **stage II.**
- A marker previously identified with poor prognosis in stage II disease — loss of heterozygosity at **18q or 18qLOH** — lost its prognostic value completely when analyzed together with **MSI** in **stage II and had no value in stage III.**

In his conclusion, the lead investigator Dr. Arnaud Roth questioned whether stage II and III colon cancers are biological different diseases rather than steps in continuous cancer development.

2009 ASCO Meeting. Roth, A.D. et al., Stage specific prognostic value of molecular markers in colon cancer: Results of the translational study on the PETACC 3-EORTC 40993-SAKK 60-00 trial. Abstract 4002.

41. Gene Mutations as Markers of Resistance to Erbitux in Chemorefractory Metastatic Colorectal Cancer (Jun. 19/09)

Kras mutations negatively affect outcome when accessing erbitux therapy. Approximately 60% of the colorectal cancer population is Kras wild type, which means they should be able to respond to anti-EGFR therapies such as erbitux. But according to these researchers, only 40% of Kras wild type respond to erbitux therapy. Therefore, it is possible that other mutations are present in the non-responding Kras wild type population. This study analyzed the Kras, Braf, Nras and PIK3CA mutations status in 276 chemorefractory (resistant to chemos) colorectal cancer treated with erbitux with or without irinotecan and showed how the mutation status was related to outcome. Progression free survival (time before cancer got worse) and overall survival were measured in patients. The results are as follows:

- **42% o**f the population was determined to be **Kras mutant (mutation in the gene)**
- Kras wild type (no mutation in that gene) was associated with an overall response, longer median progression free survival and overall survival.
- **9.8% Kras wild type** had a **Braf mutation**
- Braf wild type (no mutation in that gene) was associated with an objective response, longer median progression free survival and overall survival
- **5% Kras Wild type** had an **Nras mutation** and **no** response to erbitux therapy
- **Kras , Braf and Nras mutations were mutually exclusive;** if one was present, the others were not
- Combined Kras/Braf/Nras wild type state was associated with an objective response, longer progression free survival and overall survival
- **12%** of the population carried a **PIK3CA mutation**: 13% were responders to erbitux therapy and **11% were non-responders to erbitux therapy.** Median progression free survival and overall survival were not associated with PIK3CA mutation state overall
- Median progression free survival and overall survival were not associated with Kras/Braf/Nras wild type group

Researchers concluded that Kras, Braf and Nras mutations are mutually exclusive and occur in at least 47% of crc. Like Kras wild type, the Braf wild type gene state of the primary is significantly associated with outcome in metastatic colorectal cancer treated with erbitux. The combined Kras/Braf/Nras wild type state is significantly associated with outcome. And PIK3CA mutations occur independently of the Kras/Braf/Nras mutation status.

2009 ASCO Meeting. Lambrechts, D, et al., The role of Kras, Braf, Nras, and PIK3CA mutations as markers of resistance to cetuximab in chemorefractory metastatic colorectal cancer. Abstract #4020.

NUTRITION

42. Ginger Helps Combat Nausea in Cancer Patients (May 15/09)

Results of this study show that cancer patients can benefit from ginger supplements. University of Rochester Medical Center found that ginger could reduce nausea by **40%** when taken before chemotherapy. The study is the first to focus on using ginger combined with anti-nausea drugs to help relieve nausea associated with chemotherapy. Patients studied had a significant reduction in nausea

from taking fresh ginger three days before chemotherapy and three days after treatment. The researchers say nausea is extremely difficult to control during cancer therapy. Their findings should bring hope for cancer patients who have a difficult time controlling nausea while undergoing chemotherapy. According to lead investigator Dr. Ryan, “Nausea is a major problem for people who undergo chemotherapy and it's been a challenge for scientists and doctors to understand how to control it." Until now, only small studies have been conducted. No studies have focused on taking ginger before chemotherapy to relieve nausea. The researcher included 644 cancer patients. Four groups of patients received either placebo, 0.5 gram of ginger, 1 gram of ginger, or 1.5 grams of ginger contained in supplements, taken three days prior to and three days following chemotherapy. The cancer patients were scheduled to receive at least three rounds of chemotherapy. The results showed that cancer patients receiving chemotherapy who took 0.5g and 1.0g of ginger experienced a 40% reduction in nausea, **when combined with anti-nausea drugs**. Nausea symptoms reported by the cancer patients using ginger declined over the twenty-four hour period following chemotherapy. Dr. Ryan’s study is the first to show that ginger could be an effective and safe remedy for cancer patients undergoing chemotherapy, enhancing the effect of anti-nausea drugs.

ASCO 2009 Annual Meeting. Ryan, Julie, et al., Ginger for Chemotherapy-related Nausea in Cancer Patients. Abstract #9511.

43. Eating Vegetables is Helpful in Cancer Prevention (May 17/09)

Researchers in Italy recently published a study on how broccoli affects our bodies, as far as the cellular level, in an effort to determine why these foods are such good cancer-fighters. For this study, the researchers enrolled 20 healthy young men, half of whom were smokers. Blood samples were collected from these men during times when they were assigned to ingest approximately a cup and a quarter (200 grams) of broccoli per day and during times when they were eating no broccoli. During the broccoli diet, in both smokers and nonsmokers, damage to DNA in their blood cells decreased by an average of 22%. DNA is the genetic material inside our cells that determines how cells behave, grow, divide and die. Minimizing damage to DNA is important because it is believed that DNA damage is a key step in the development of all types of cancer. Also, in the smokers, broccoli decreased a marker of oxidation by about 51%. This is important because oxidation (oxidative stress) is one of the things that may damage DNA. The researchers concluded that something as simple as eating broccoli may help protect us against cancer. Broccoli is a cruciferous vegetable. Cruciferous refers to the group of vegetables belonging to the mustard family and also includes cauliflower, cabbage, Brussels sprouts, kale, chard, kohlrabi, bok choy, collard greens, turnips, rutabaga, mustard greens, radishes, daikon root (similar in taste to a radish, but looks like a white carrot), water cress, and horse radish. The study advocates on behalf of eating these foods regularly. The goal is to aim for 4-6 times per week, which means eating some of these foods on most days. Cruciferous vegetables have been consistently shown, with research, to have cancer-fighting properties (anti-oxidant properties and chemoprotective properties). For people concerned about cancer prevention, previous studies support that a vegetable-rich diet is a positive way to reduce cancer risk. Even after a cancer diagnosis, improving diet by eating more nutrient-rich vegetables appears to provide benefit: People with healthier diets have improved survival, even after you take into account factors such as age, gender, type of cancer, stage of cancer, and treatment received. New research on this topic now is shedding light on *how* certain vegetables actually may protect against cancer.

Riso, Patrizia, et al., Effect of Broccoli intake on markers related to oxidative stress and cancer risk in healthy smokers and nonsmokers. Nutrition and Cancer. Vol. 61, Issue 2, pp. 232-237.

44. Green Tea for Cancer Prevention (May 21/09)

Because of the lower incidence of certain cancers in societies where green tea drinking is common (Japan, Korea, and China, for example), green tea has been studied in the laboratory for its preventive effects against experimental cancers. The results have universally shown that green tea can prevent many types of cancers in mice and rats. Because of this finding, green tea has been examined for its content of cancer-reducing chemicals. The phytochemicals in green tea include catechins as well as the major chemical EGCG (epigallocatechin gallate). When experiments have been performed with this very active chemical, EGCG was shown to induce programmed cell death (apoptosis) in cancer cells growing in culture, and also reduce cancer cell growth in test tubes. It also was found to reduce growth receptors on cancer cells, so that cancer cells could not grow in response to chemicals that stimulate cancer cell reproduction. To further demonstrate the activity of green tea or green tea chemicals in people, in this recent study, researchers tested green tea extracts in the prevention of pre-cancerous growths in the **colon and rectum**. They studied 136 patients who had a prior growth (polyp or adenoma) removed at colonoscopy, and were still free of polyps one year later. Then, physicians randomly gave these individuals either continuation of usual habits, or supplementation with additional green tea extract. The patients then had a repeat colonoscopy 12 months later to determine how many pre-cancerous colon polyps had developed. In patients who had received additional green tea extract, there was a 51% reduction in the number of pre-cancerous adenomas in just 12 months. In addition, compared to the group that had no additional green tea extract, the size of these pre-cancerous growths that were detected were much smaller if patients had received green tea extract. The degree of reduction in size was from 4.0 mm with usual diet and activities down to 3.0 mm with green tea extract.

45. Red Meat and the Link to Cancer (May 25/09)

The *American Journal of Clinical Nutrition* published two studies on the relationship between meat and colon cancer this month. The first was a meta-analysis or a re-analysis of data obtained from previously conducted studies. **It found no association between meat and colorectal cancer.** The lead investigator from that study concluded: "The available epidemiologic evidence does not appear to support an independent association between animal fat intake or animal protein intake and colorectal cancer." Perhaps something to bear in mind is the fact that the study was funded by the US National Pork Board and US National Cattlemen's Beef Association. The second study, on the other hand, **did find an association. Compounds in cooked meat raised the risk of colon cancer.** There, the lead investigator concluded: "The results support data from case-control studies of a positive association between HCA intake and colorectal adenoma risk." (HCAs are Heterocyclic Aromatic Amines that come from cooking meat or fish at high temperatures.) "Adenoma risk also increased with the consumption of strongly or extremely browned meat." This second study was funded by Kurt-Eberhard-Bode Foundation, which promotes medical and science research, and the European Commission and German Cancer Aid. This study, unlike the first, was an original epidemiological study of a German subset (25,540 participants) of the European EPIC prospective cohort.

Alexander, Dominik, et al., Meta-analysis of animal fat or animal protein intake and colorectal cancer. American J of Clin Nutrition. Vol. 89: pp. 1402-1409.

Rohrmann, Sabine, et al., Heterocyclic aromatic amine intake increases colorectal adenoma risk: findings from a prospective European cohort study. Amer J of Clin Nutrition. Vol. 89: pp. 1418-1424.

46. Certain Supplements Lower Colon Cancer Risk (May 31/09)

Results recently published from the Vitamins and Lifestyle Study suggests that certain dietary supplements may have an effect on colorectal cancer risk. This type of research is very important because so many people take dietary supplements and little is known about how long-term use of these products may affect cancer risk. Researchers enrolled approximately 78,000, 50-76 year old men and women from Western Washington State, each of whom completed an extensive, 24-page questionnaire on dietary supplement use when joining the study. After studying this group for ten years, the researchers compared people who reported ever using certain dietary supplements with those who reported never using these supplements and found the following:

- People using glucosamine had **27% *lower*** risk of colorectal cancer.
- People using chondroitin had **35% *lower*** risk of colorectal cancer.
- People using fish oil had **35% *lower*** risk of colorectal cancer.
- People using a supplement called MSM (methylsulfonylmethane) had **54% *lower*** risk of colorectal cancer.
- People using the herb St. John's wort had **65% *lower*** risk of colorectal cancer.
- People using garlic pills had **35% *higher*** risk of colorectal cancer.

This research was an observational study. Observational studies cannot prove cause and effect. They simply show an association between two things, in this case, using a supplement and risk of colorectal cancer. This does not necessarily mean that the supplement caused cancer risk to be reduced. It may merely mean these two things occurred together. Supplement users may also eat a healthier diet, exercise more, or do other things that non-supplement users don't do. It may be that the true reason for the lowered risk of colon cancer in supplement users is that these *other,* unaccounted for*, health behaviors* also reduce risk. It may not be the supplements at all, or on the other hand, it may very well be. And even though researchers adjust their findings to "control for" these other factors, there is no way to know if they've considered them all. Researchers did conclude that additional studies examining the effects of herbal/specialty supplements on risk for cancer and other diseases are required.

Satia, Jessie, et al., Associations of Herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. Cancer Epidemiology, Biomarkers & Prevention. 2009; Vol. 18, Issue 5: pp. 1419-1428.

47. Alcohol and Smoking Cause Colon Cancer (Jun. 3/09)

A new study has found that lifestyle risk factors such as alcohol consumption and cigarette smoking are important risk factors for bowel cancer. Researchers have shown that people who consume the largest quantities of alcohol (equivalent to > 7 drinks per week) have 60% greater risk of developing the cancer, compared with non-drinkers. **Smoking**, **obesity and diabetes** were also associated with a 20% greater risk of developing bowel cancer - the same risk linked with consuming high intakes of red and processed meat. According to lead researcher, the most startling finding of this study was, "The strong, and largely, unknown association between high intakes of alcoholic beverages with risk of colorectal cancer. Most people probably know that being overweight and having poor dietary habits are risk factors for the disease, but most are probably unaware that other lifestyle risk factors such as alcohol consumption,

cigarette smoking and diabetes are also important culprits." Researchers also demonstrated that physical activity lowered an individual's risk of the disease but surprisingly, there was little evidence to indicate that high intakes of fruit and vegetables were protective against bowel cancer.

The George Institute for International Health, news release, June 2, 2009 id=627710
www.thegeorgeinstitute.org/events/latest-news/strong-link-between-obesity-and-colorectal-cancer.cfm

48. Calcium & Colorectal Cancer (Jun. 8/09)

According to this study, people who consume more calcium and dairy foods have a lower risk of colon cancer. Researchers collected diet and other information on more than 500,000 people aged 50 to 71. After seven years, the risk of colorectal cancer was approximately 20% lower in men who consumed the most calcium from food and supplements (roughly 1,500 milligrams a day) than in men who consumed the least (roughly 500 mg a day). The risk was about 30% lower in women who consumed the most calcium (roughly 1,900 mg a day) than in women who consumed the least (roughly 500 mg a day). Colorectal cancer risk was also lower in men or women who ate the most dairy foods. Dairy wasn't linked to a higher risk of ovarian cancer, and calcium wasn't linked to a higher risk of prostate cancer as some earlier studies had suggested. Currently, the recommendations are to aim for 1,000 mg a day of calcium if you're 50 or younger and 1,200 mg a day if you're over 50 years of age. You may assume that you're obtaining roughly 300 mg from each serving of milk, cheese, yogurt, or calcium-fortified orange juice. Given the earlier studies linking high calcium intake to an increased risk of prostate cancer, men may wish to adhere to the 1,200 mg dosage accordingly so as to err on the side of caution. Researchers maintain that a link exists between calcium intake and colorectal cancer risk.

Park, Y, et al., Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. Archives of Internal Medicine. 2009, Volume 169, Issue 4, Pages 391-401

49. Vitamin D and Cancer Prevention (Jun. 17/09)

There are a number of associated reports involving studies of vitamin D and cancer prevention appearing in this issue of Annals of Epidemiology. Researchers maintain that higher serum levels of the main circulating form of Vitamin D known as 25-hydroxyvitamin D [25(OH)D] are associated with substantially lower incidence rates of colon cancer, as well as other types of cancer. Researchers maintain that Vitamin D prevents disjunction of cells (the very first phase wherein cells begin to go awry in the process of carcinogenesis – formation of cancer) and are beneficial in other phases as well. Researchers believe that raising the minimum year round serum of vitamin D level from 40 to 60 ng/ml, by ingesting 2000 IU (international units) per day, would prevent approximately 49,000 new cases of colorectal cancer each year and three fourths of death, in the US and Canada, based on observational studies combined with a randomized trial. Such intakes are also expected to reduce fatality rates of patients who already have colorectal cancer by half. The study continues by reassuring consumers that there are no unreasonable risks from intake of 2000 IU per day of vitamin D3, or from a population serum 25(OH)D level of 40-60 ng/ml. **The researchers conclude by advocating on behalf of a nationally coordinated action to substantially increase intake of vitamin D and calcium.**

Garland, C F., et al., Vitamin D for Cancer Prevention: Global Perspective – Annals of Epidemiology, July 2009. Annals of Epidemiology. July 2009; Vol. 19, Issue 7, pp. 468-483.