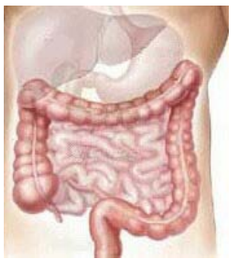
COLORECTAL CANCER RESEARCH

Month Ending September 18, 2009



The following colorectal cancer research update extends from August 15 –September 18, 2009 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Expensive Colorectal Cancer Drugs Deemed Worthy by Study (Aug. 17/09)

The cost for chemotherapy medications to treat colorectal cancer for six months has jumped 2,600% from 1993 to 2005. But such rising costs are worth the price, asserts a new report from Cornell, when improved longevity and quality of life are taken into account. Four methods were used to compare the costs and benefits of newer chemotherapy medications for colorectal cancer, whose costs rose to $36,300 in 2005 from $127 in 1993 for a six-month treatment, against older, cheaper medications (2600% rise). They took into account life expectancy, tumor responses and side effects, using data from thousands of colon cancer patients and treatment decisions by oncologists nationwide. The new drugs -- which are often used in combination and include Avastin, Oxaliplatin and leucovorin -- improve survival rates by almost 100% (to 23.2 months from 12.5 months), and patients taking the newer drugs often experience fewer side effects, the researchers report in a working paper issued by the National Bureau of Economic Research in July.

www.physorg.com/news169480097.html

2. Adding Vectibix to Folfiri Improved Progression Free Survival (Aug. 18/09)

Amgen announced positive top-line results from a Phase 3 trial evaluating Vectibix in combination with FOLFIRI (an irinotecan-based chemotherapy) as a second-line treatment in 1,186 patients with metastatic colorectal cancer (mCRC). The endpoints tested were progression-free survival and overall survival. Vectibix significantly improved progression-free survival in combination with FOLFIRI, compared to FOLFIRI alone, in patients with Kras wild type metastatic colorectal cancer. The adverse event profile was as anticipated for an anti-EGFR therapy in combination with irinotecan-based chemotherapy, including known events such as skin toxicity, diarrhea and hypomagnesemia (diminished magnesium levels). These results will be presented at Europe's largest cancer conference, ECCO 15 – ESMO in the month of September.

http://www.medicalnewstoday.com/articles/160901.php

3. Medical Treatment of Advanced Colorectal Cancer in 2009 (Aug. 21/09)

This study outlines how oncologists now integrate conventional cytotoxic agents such as oxaliplatin and irinotecan (which directly fight tumour cells) with treatments such as bevacizumab (avastin) and epidermal growth factor receptor (EGFR) antibodies, cetuximab and panitumumab, as novel targeted agents into standard medical therapy. The result is that median overall survival in metastatic CRC now exceeds two years for the first time. For decades, standard first-line therapy consisted of the drugs fluorouracil (5-FU) plus leucovorin, which helped just a fifth of patients to survive a median of one year. In the late 1990s and early 2000s, the addition of oxaliplatin and irinotecan to the backbone of 5-FU and leucovorin led to dramatic improvement in median survival to nearly 24 months. Most recently, biologic agents such as bevacizumab, cetuximab, and panitumumab, have yielded even better results for many patients. It cannot be overemphasized that these significant improvements in outcome of patients with CRC are closely linked to the number of active drugs available to treat this disease. One targeted agent is bevacizumab (a monoclonal antibody under the trade name Avastin), which inhibits vascular endothelial growth factor (VEGF), a natural protein that the tumour uses to grow new blood vessels (angiogenesis). Bevacizumab was the first angiogenesis inhibitor available and has become established as a standard component of first-line chemotherapy. To date, no researchers have identified a predictive marker for bevacizumab's activity in metastatic CRC. According to Grothey, the lead researcher, key questions surrounding bevacizumab's use in the palliative setting are whether it provides clinical benefit beyond the stage of tumour progression, and which patient group is at higher risk for bevacizumab-related toxicities. Anti-epidermal growth factor receptor (EGFR) antibodies cetuximab (Erbitux) and panitumumab (Vectibix) are both targeted monoclonal antibody treatments that have demonstrated efficacy both in combination with chemotherapy or, in contrast to bevacizumab, used alone. Trials show limited results. But clinical trials and translational studies now indicate that those patients with advanced CRC must have a tumour with specific genetic mutations (wild type KRAS and wild-type BRAF) for EGFR antibodies to be effective. Testing for BRAF and KRAS mutations now excludes about half of patients

with CRC from an ineffective, but potentially harmful (and expensive) therapy with cetuximab and panitumumab. Clinical decisions regarding whether the goal is to rapidly shrink a tumour, whether to attempt curative surgery or to rapidly boost short-term quality of life or survival, or instead aiming for a longer-term quality of life with minimum side effects will determine the physician's choice of approach, according to the investigator.

Grothey, A., et al., Medical Treatment of advanced colorectal cancer in 2009. Therapeutic Advances in Medical Oncology (2009): 0(0); pp.1-14. DOI: 10.1177/ 1758834009343302

4. Hormone Replacement & Colorectal Cancer Risk (Aug. 26/09)

Postmenopausal women receiving hormone replacement therapy (HRT) reduce their risk of developing colorectal cancer by more than half, according to this study. Researchers compared the self-reported use of HRT from 2,460 peri/postmenopausal women among 2,648 patients with colorectal cancer and 2,566 controls. After adjusting for demographics, aspirin and statin use, sports activity, family history of colorectal cancer, and vegetable consumption, the researchers found that women reporting HRT use had a significantly lower risk of colorectal cancer. Women who took aspirin or played sports did not have a risk reduction. The reduced risk was observed mainly in women taking combined estrogen-progestin oral pills. The use of oral HRT was associated with a 63% relative reduction in the risk of colorectal cancer in postmenopausal women after adjustment for other known risk factors as previously mentioned. However, the absence of the risk reduction effect of aspirin in HRT users call for further studies to understand the causes of these phenomena and calls for caution in indicating HRT for colorectal cancer prevention.

Rennert, Hedy S., et al., use of Hormone Replacement Therapy and the Risk of Colorectal Cancer. J of Clin Oncology; JCO Early Release, published online ahead of print Aug. 24, 2009. DOI: 10.1200/JCO.2009.22.0764

5. Guidance on the Use of Erbitux (Cetuximab) (Aug. 26/09)

The National Institute for Health and Clinical Excellence (NICE) has published final guidance on the use of cetuximab (erbitux) for the first-line treatment of metastatic colorectal cancer. The guidance recommends the following:

1. Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:
    - The primary colorectal tumour has been resected or is potentially operable.
    - The metastatic disease is confined to the liver and is unresectable.
    - The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
2. Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, for the first-line treatment of metastatic colorectal cancer when the 3 criteria listed above are met and the patient is unable to tolerate or has contraindications to oxaliplatin.
3. Patients who meet the above criteria should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.
4. People with metastatic colorectal cancer whose metastatic disease is confined to the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialized liver surgical services.

http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=7688

6. Methotrexate Shows Promise in Treating HNPCC (Aug. 29/09)

Scientists at The Institute of Cancer Research (ICR) in London have shown that a chemotherapy drug invented in the 1940s has the potential to work against a genetic condition linked to bowel and other cancers. HNPCC is a hereditary condition involved in approximately 5% of all bowel cancer cases. It also puts people at increased risk of developing stomach, womb, ovarian, kidney and other cancers. Almost 40% of people with HNPCC have a faulty MSH2 gene, so scientists at the Breakthrough Breast Cancer Research Centre at the ICR in London looked for drugs that selectively kill cells containing this damaged gene. They tested a range of drugs on cells with the faulty MSH2 gene and found a drug called methotrexate destroyed the cells particularly well. Methotrexate is similar to a normal molecule called folinic acid, which is required for copying DNA. The drug prevents cells from making and repairing DNA - a process needed for cancer growth. Methotrexate was one of the first chemotherapy drugs to be invented in the 1940s and is still used to treat a number of cancers today. But until now, it has not commonly been used to treat people with HNPCC. MSH2 usually plays an essential role in repairing DNA damage. When the gene is damaged, mistakes in the genetic code of cells increase the risk of

cancer. Methotrexate selectively destroys cells lacking the MSH2 function, providing a targeted therapy for patients with bowel cancer caused by MSH2 mutation.

http://www.emaxhealth.com/2/51/33175/old-drug-shows-promise-inherited-cancer.html

7. Targeting The "Hedgehog" Pathway May Create New Therapies for Colorectal Cancer (Aug. 31/09)

Scientists in Switzerland have discovered a way to block the growth of human colon cancer cells, preventing the disease from reaching advanced stages and the development of liver metastases. The research shows that blocking the so-called Hedgehog-GLI (HH-GL1) pathway can prevent the growth of tumours, metastatic lesions and cancer stem cells, the cells thought to lie at the root of cancer growth. Colon cancer often begins in a treatable form when it is confined to the bowel wall, but in frequent cases it can develop to an incurable metastatic stage. A Geneva-based research team has discovered the essential role played by HH-GLI in the progression of colon cancer to these late and incurable stages. HH-GLI is a signaling pathway used by cells to communicate with each other, often used to determine position, growth and survival. In this study they have proven that HH-GLI is essential for the development and growth of colon cancers. The research demonstrates the active presence of HH-GLI signaling in epithelial cells of colon cancers. Moreover, they found that metastatic tumours rely on this pathway for sustained growth. This identifies HH-GLI as a target for novel anti-cancer therapies against so far incurable forms of colon cancer in distant organs, such as the liver. This research opens the possibility of new anti-cancer therapies, specifically the use of RNA interference and of Cyclopamine, a plant product known to block Hedgehog pathway activity. This and other similar molecules can now be considered for future research as a treatment for terminal patients with metastatic disease and to fight resurgent forms of the disease.

Varnat, F., et al., Human colon cancer epithelial cells harbour active Hedgehog-GLI signaling that is essential for tumour growth, recurrence, metastasis and stem cell survival and expansion. EMBO Molecular Medicine, July 2009.

8. Xeloda (Capecitabine) In Combination with Oxaliplatin or Irinotecan Well Tolerated in Elderly (Sept. 1/09)

This study sought to determine the efficacy and toelratiblity of capecitabine (xeloda) combined with oxaliplatin (capox) or irinotecan (capiri) as first line treatment in patints with advanced metastatic colorectal cancer who where 70 years or older. Patients received either capox or capiri. The primary study end point was overall response rate. From the 94 patients enrolled, there were 2 complete responses and 16 partial responses on capox (38% response rate) and 2 complete responses along with 15 partial responses on capiri (36% response rate). Time to progression (time before disease got worse) on capox was 8 months vs. 7 months for capiri and overall survival on capox was 19.3 months vs. 14 months on capiri. Researchers concluded that capox and capiri had similar efficacy in the elderly, although capox appeared to be better tolerated.

Rosati, G. et al., Capecitabine in combination withoxaliplatin or irinotecan in elderly patients with advanced colorectal cancer: results of a randomized phase II study. Annals of Oncology. Advance Access published online on August 27, 2009. DOI: 10.1093/annonc/mdp359

9. Drug Could Address Skin Toxicity Resulting from Anti-EGFRs (Erbitux and Vectibix) (Sep. 3/09)

This study sought to determine if there could be a way around the harsh skin toxicity associated with a widely used cancer drug. Cetuximab (Erbitux) is a monoclonal antibody that binds to and inhibits the epidermal growth factor receptor (EGFR). It is widely used to treat colorectal cancer. Although cetuximab and other EGFR inhibitors are associated with a lower rate of side effects compared with conventional chemotherapy, adverse effects of the drugs often include a dose-limiting skin rash and gastrointestinal symptoms. Adverse events in antibody therapy are frequently due to the binding of antibodies to normal tissue in addition to tumor tissue. By "masking" the antibodies so they preferentially bind to the tumor tissue, the toxicity may be reduced or avoided. A prodrug has been designed in which the antibody is masked by an engineered form of the receptor protein, preventing it from binding to the antigen on normal tissue. However, when the antibody reaches the tumor tissue, enzymes prevalent at tumor sites cleave the mask off, and the antibody can now engage the receptor at the tumor site. The prodrug contains the receptor binding sites of two different EGFR-specific antibodies: 425 (matuzumab) and C225 (cetuximab). Each antibody is connected via peptide linker to the receptor. The linkers contain sites susceptible to proteolytic cleavage (cutting using a protein) by metalloprotease 9 (MMP-9), an enzyme that is frequently over-expressed in epithelial malignancies such as colorectal cancer. Cleavage of the complex leads the antibodies to become "unmasked" and able to bind to the receptors on the tumor cells. This work provides proof-of-principle evidence that the concept is feasible, and sets the stage for future studies using tumors grown in vivo (in animals or humans).

http://www.jefferson.edu/news/news.cfm?artid=/news/2009/article18381.html

10. S-1 Combined with Irinotecan to Treat Advanced Colorectal Cancer (Sept. 8/09)

This study sought to determine the efficacy and tolerability of oral fluoropyrimidine S-1 plus irinotecan in patients with previously untreated advanced colorectal cancer. S-1 was administered orally for 21 consecutive days followed by a 2-week rest. CPT-11 was given intravenously on days 1 and 15 of each course. Courses were repeated every 5 weeks, unless disease progression or severe toxicities were observed. A total of 282 courses of treatment were administered to 40 patients, achieving complete response in 1 and partial responses in 24 with an overall response rate of **62.5%.** Median progression-free survival (time before disease got worse) was 7.8 months. The rates of grade 3 or 4 toxicities were as follows: neutropenia 12.5%, anorexia 12.5%, fatigue 10%, and diarrhea 7.5%. Researchers concluded that combined treatment with S-1 and irinotecan is an effective, well-tolerated and convenient regimen in patients with advanced colorectal cancer which is easily maintained.

Tsunoda, A., et al., Phase II Study of S-1 Combined with Irinotecan (CPT11) in Patients with Advanced Colorectal Cancer. Oncology. Vol. 77, No. 3-4, 2009.

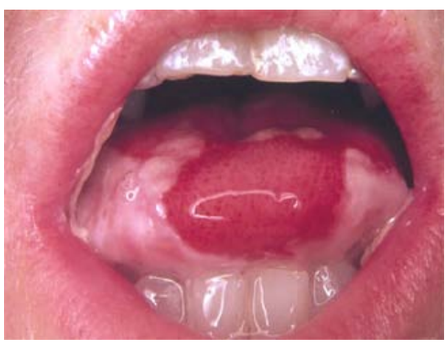
11. Predicting Avastin (Bevacizumab) Efficacy Using Biomarker CA19-9 in Metastatic Colorectal Cancer (Sept. 9/09)

CEA and CA19.9 are biomarkers routinely measured for monitoring treatment response in metastatic colorectal cancer (MCRC) patients, yet their predictive value during therapies containing new drugs (i.e. FOLFIRI/OLFOX/Bevacizumab) has not yet been investigated. Chemotherapy-naive MCRC patients treated with either standard chemotherapy alone (FOLFIRI/FOLFOX) or chemotherapy + avastin (FOLFIRI+bevacizumab) were included in the analysis. Patients had to have serial (blood) biweekly measurement of CEA and CA19.9 available for at least three months of treatment. Primary study endpoint was Progression Free Survival (PFS - time before disease got worse). Biomarker levels and type of treatment as well as major demographic and clinical factors were analyzed for their impact on PFS. Out of 243 evaluated MCRC patients, 87 had biomarkers available as per inclusion criteria. Among all evaluated factors only type of treatment (chemotherapy-alone vs chemotherapy + bevacizumab) and baseline CA19.9 (greater than normal vs. less than normal) were independently associated with PFS. When patients with different baseline CA19.9 levels were analyzed separately, only patients with abnormal CA19.9 benefited significantly from the administration of bevacizumab. The current study demonstrated a significant predictive value of CA19.9, but not of CEA and biomarker reduction, for MCRC patients treated with new drugs. Moreover, only patients with abnormal baseline CA19.9 levels benefited significantly from bevacizumab.

Formica, V. et al., Role of CA19.9 in predicting bevacizumab efficacy for metastatic colorectal cancer patients. Cancer Biomarkers. Vol. 5, No. 4-5, 2009. pp. 167-175

12. Results for Prophylactic Use of rhITF in Mucositis (Sept. 9/09)

This study evaluated the safety and efficacy of recombinant human intestinal trefoil factor (rhITF) administered as topical oral spray for prevention and treatment of chemo-induced oral mucositis. rhITF oral spray is being developed for the treatment and prevention of oral mucositis (OM). Oral mucositis can be a serious, oral complication of high-dose systemic chemotherapy and radiation-based anti-cancer treatments, and can lead to hospitalization, infection and/or interruptions in the administration of cancer therapy. These cytotoxic therapies (chemos and radiotherapy) are used to kill cancer cells, but they also indiscriminately kill other fast-growing normal cells such as those lining the inside of the mouth and throat. Oral mucositis is an inflammation of the mucosa of the mouth which ranges from redness to severe ulcerations on the inner cheek, tongue and lips. These debilitating oral sores further diminish quality of life by preventing patients from eating, drinking, or talking for weeks at a time. These conditions can reappear after every course of treatment. In addition to extremely painful open oral sores, patients with oral mucositis typically have diminished immunity resulting from chemotherapy and / or radiotherapy and are prone to serious life-threatening opportunistic infections. Results of this Phase II study demonstrate that rhITF oral spray formulation is safe and highly effective in the prophylaxis of chemotherapy-induced OM in colorectal cancer patients. Patients also exhibited high compliance in dosing administration. The investigators concluded that future clinical studies are warranted in order to develop this important new compound for therapeutic use in OM patients.



Severe Oral Mucositis

Typically, oral mucositis symptoms develop 5 to 8 days following the administration of Chemotherapy and last approximately 7 to 14 days.

Source:
http://images.google.com/imgres?imgurl=http://www.kepivance.com/images/etiology01.jpg&imgrefurl=http://www.kepivance.com/oral_mucositis/etiology.jsp&usg=__ZBcoNFt7DdreGTgRzdUAjakMhTM=&h=243&w=324&sz=31&hl=en&start=2&sig2=XNHEw1A84_MfPl34DoMhsw&um=1&tbnid=G35EVTgArwjJIM:&tbnh=89&tbnw=118&prev=/images%3Fq%3DMUCOsitis%26hl%3Den%26sa%3DN%26um%3D1&ei=RjuxSrecM8Pi8Qan3sSlDA

Peterson, Douglas, et al., Phase II randomized double-blind, placebo-controlled study of recombinant human intestinal trefoil factor oral spray for prevention of oral mucositis in patients with colorectal cancer who are receiving fluorouracil-based chemotherapy. J of Clinical Oncology, Vol 27, No. 26 (September 10, 2009): pp. 4333-4338

13. Amphiregulin and Epiregulin Expression Predicts Outcome in mCRC Treated with Erbitux (Sept. 11/09)

This study investigated the power of the epidermal growth factor receptor (EGFR) **epiregulin** (EREG) and **amphiregulin** (AREG) and their expression in primary tumors to predict the outcome in patients with chemorefractory (resistant to chemo) metastatic colorectal cancer (cmCRC) treated with the combination of cetuximab (erbitux) and irinotecan. Gene expression measurements and *KRAS* mutation analysis were performed on stored primary tumors of 220 cmCRC patients. In *KRAS* wild type (WT) patients, there was a significant association between expression of these two molecules and response for EREG and for AREG. Expression was significantly associated with progression-free survival (PFS) and overall survival (OS). There was no predictive power of expression of these two molecules in patients with *KRAS* mutation. Researchers concluded that expression of EGFR ligands (epiregulin and amphiregulin) in primary tumors significantly predicts outcome in *KRAS* WT mCRC treated with cetuximab and irinotecan who are resistant to chemo.

Jacobs, B et al., Amphiregulin and Epiregulin mRNA expression in primary tumors predicts outcome in metastatic colorectal cancer treated with cetuximab. J of Clinical Oncology. JCO Early Release, published online ahead of print Sept. 8, 2009. DOI: 10.1200/JCO.2008.21.3744

14. New Study Testing Aviscumine in Metastatic Colorectal Cancer Patients Who Are Chemo-Resistant (Sept. 15/09)

Cytavis GmbH in Germany has commenced phase II testing of its apoptosis inducer (cell death inducer) **Aviscumine** (CY-503) in patients with chemotherapy-refractory metastatic colorectal carcinoma (NCT 00932724). The multicentre study will include more than 200 patients with progressing metastatic colorectal cancer after failure of chemotherapeutic standard treatments. The primary endpoint will be progression-free survival; secondary endpoints will be overall survival, safety, and quality of life. In addition, the effect of Aviscumine on a number of immune functions will be assessed. The company's lead compound, which has been already tested in three phase I cancer trials, is a recombinant version of viscumin, a protein found in the mistletoe plant. It targets the CD75 receptor on cancer cells and kills them with a cytotoxic protein that acts as an apoptosis inductor through inactivation of protein biosynthesis. According to the company, the molecule also acts as an immunostimulant for natural killer (NK) cells and neutrophil granulocytes.

http://www.eurobiotechnews.eu/service/start-page/top-news/?tx_ttnews%5Btt_news%5D=11331

SURIGCAL THERAPIES

15. Lung Mets Resection Can Prolong Long Term Survival in mCRC Patients (Aug. 21/09)

According to this study, patients with low tumor markers and no lymphatic invasion can expect good long-term survival after resection of lung metastases from colorectal cancer. Furthermore, the results suggest that patients with multiple lung metastases can be salvaged by repeated complete pulmonary resection (RO). Researchers in Japan reviewed the records of 113 patients who underwent R0 resections of pulmonary metastases from colorectal cancer, hoping to identify factors that predict good survival. At a median follow-up of 49 months, the overall 5-year survival rate was 67.8%, the authors report. Preoperative serum (blood) levels of carcinoembryonic antigen (CEA) and lymphatic invasion by pulmonary tumor were independent prognostic factors for survival. Five- and 7-year survival rates were 80% and 60%, respectively, for patients with preoperative CEA levels below 5 ng/mL. For patients with no lymphatic invasion by pulmonary tumor, 5- and 7-year survival rates were 75% and 62%, respectively. For patients who met both criteria, 5- and 7-year survival rates were 94% and 79%, respectively, the investigators say, which indicates a much better prognosis than in patients with a higher CEA level and/or lymphatic invasion. Repeat pulmonary resection was not predictive of 5-year survival. This study is based on the patients with surgery alone. Researchers believe that further study is required to evaluate whether adjuvant chemotherapy after resection of the pulmonary metastases may improve overall survival or local disease-free survival.

Watanabe, K., et al., Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. British J of Surgery. Vol. 96, Issue 9, pp. 1058-1065

16. New Data On Primary Tumor Resection for Stage IV Colorectal Cancer Patients (Sept. 3/09)

The benefit of elective primary tumor resection for non-curable stage IV colorectal cancer (CRC) remains largely undefined. Researchers in this German study wished to identify risk factors for postoperative complications and short survival. Using a prospective database, researchers analyzed potential risk factors in 233 patients, who were **electively** operated for non-curable stage IV CRC between 1996 and 2002 with recurrent tumors, resectable metastases, emergency operations, and non-resective surgeries were excluded. Risk factors for increased postoperative morbidity and limited postoperative survival were identified. Palliative resection was associated with a particularly unfavorable outcome in rectal cancer patients presenting with a locally advanced tumor or an extensive comorbidity, and in all CRC patients who show a hepatic tumor load > 50%. The researchers concluded that for such patients, surgery might be contraindicated unless the tumor is immediately life-threatening.

Kleespies, A., et al., Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. International J of Colorectal Disease. 2009; 24(9): pp.1097-1109.

17. Difficulties with Endoscopic Removal of Submucosal Colorectal Tumors (Sept. 10/09)

Endoscopic submucosal dissection (ESD) is an advanced endoscopic procedure designed to resect early colorectal tumors. Endoscopic submucosal dissection (ESD) for colorectal tumors is not generally recommended because of the technical difficulties and complications associated with the removal, including perforation. These aspects of ESD were analyzed in this retrospective study. Researchers studied 105 colorectal tumors, from 100 patients, that were treated by ESD at the Kyoto Prefectural University of Medicine or Nara City Hospital between 2005 and 2008. They analyzed tumor size, operation time, rate of en bloc resection (removal of tumor in one piece), and complications. In addition, they thoroughly investigated the cases of perforation. The average tumor size was 30.4 mm; average operation time, 102 min; and rate of en bloc resection, 88.5 %. Perforation occurred in 10.4 % of the ESD procedures. Of the 11 perforations, 8 were detected during ESD and treated by clip closure during endoscopy, while 3 were evident only on subsequent routine CT scan which were managed conservatively. A case of postoperative hemorrhage was also observed. Researchers concluded that ESD effectively achieved a high rate of en bloc resection. However, the perforation rate was substantial; hence, improvement in the ESD method is required. The outcomes of ESD, especially for early colorectal malignancies, require further assessment.

Yoshida, N. et al., Endoscopic Submucosal dissection for colorectal tumors: technical difficulties and rate of perforation. Endoscopy. 2009 September; 41(9): pp. 758-761.

RADIATION / INTERVENTIONAL RADIOLOGY

18. Administration of PET Reduces Futile Liver Mets Resections (Aug. 17/09)

Researchers from the Netherlands have reported that the use of 18F-FDG PET scans reduced the number of futile surgeries for hepatic mets from 45% to 28%. According to the study, use of 18F-FDG PET imaging can reduce the rate of futile surgeries in patients with colorectal liver metastases. This is the first and only randomized controlled clinical trial on the efficacy of FDG-PET to select patients with liver metastases from colorectal cancer for liver surgery. According to the researchers, the biggest finding is that FDG-PET detects additional disease that deems liver surgery futile in 1 in 6 patients, who would have been taken to surgery when CT alone was used. Furthermore, the addition of FDG-PET in every patient did not result in an increase of overall health care costs. The results stem from a study of 150 patients with colorectal liver metastases who were randomly assigned to preoperative evaluation with CT alone or CT combined with FDG-PET. The subjects were followed for at least 3 years after randomization. **Futile surgery**, the main outcome measure, **was defined as a surgery that did not lead to complete tumor removal, showed benign disease, or that did not improve disease-free survival by longer than 6 months**. 34 patients (45%) in the control group had a futile surgery compared with 21 (28%) in the PET group, a risk reduction of 38%. Lead researcher emphasized that every patient with liver metastases from colorectal cancer to whom liver surgery is offered, should ask for FDG-PET before the final decision to actually go ahead with liver surgery is made. Researchers added that future research will focus on the role of neoadjuvant (presurgical) chemotherapy and the role of novel surgical procedures such as radiofrequency ablation of tumors.

Oyen, Wim J.G., et al., Improved selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: A randomized study.* Journal of Nuclear Medicine. *2009;50:1036-1041

19. Three-Staged SRT for Large Metastatic Brain Tumors (Sept. 1/09)

This study sought to evaluate the efficacy and toxicity associated with staged stereotactic radiotherapy (SRT) for unresectable brain metastases more than 10 cm3 in volume. Subjects included 43 patients

(24 men and 19 women), ranging in age from 41 to 84 years, who had large brain metastases (> 10 cc in volume). Primary tumors were in the colon in 14 patients, lung in 12, breast in 11 and other in 6. The peripheral dose of SRT was 10 Gy in three fractions. The interval between fractions was 2 weeks. The mean tumor volume before treatment was 17.6 ± 6.3 cm3. Mean follow-up interval was 7.8 months. The local tumor control rate, as well as overall, neurological, and qualitative survivals, were calculated. At the time of the second and third fractions, mean tumor volumes were 14.3 ± 6.5 (**18.8% reduction**) and 10.6 ± 6.1 cm3 (**39.8% reduction**), respectively, showing significant reductions. The median overall survival period was 8.8 months. Neurological and qualitative survivals at 12 months were 81.8% and 76.2%, respectively. Local tumor control rates were **89.8% and 75.9% at 6 and 12 months**, respectively. Tumor recurrence-free rate at 12 months was 80.7%. Researchers concluded that the 2-week interval allowed significant reduction of the treatment volume and results suggest staged stereotactic radiotherapy using this protocol to be a possible alternative for treating large brain metastases.

NB: SRT is a type of external beam radiation therapy that can be completed in one to five days rather than several weeks (see image below). SRT is best for very small tumors. Doctors use very specialized imaging equipment (see image below) to pinpoint exactly where the cancer cells are. Doctors monitor the area of the cancer and other organs on a screen while treatment is taking place.

Stereotactic Radiation Therapy

Source: *http://images.google.com/imgres?imgurl=http://cancerclubcisc.files.wordpress.com/2009/02/stereotactic-radiation-therapy.jpg&imgrefurl=http://cancerclubcisc.wordpress.com/2009/02/14/more-about-stereotactic-radiation-therapy/&usg=__P2T5Mh3HMpbvPK_pnO7Xxkfr_wk=&h=225&w=300&sz=15&hl=en&start=1&sig2=zk23tOOHjPt1kUeb4Ycypw&tbnid=E7KRUQC50GlTMM:&tbnh=87&tbnw=116&prev=/images%3Fq%3Dstereotactic%2Bradiation%2Btherapy%26gbv%3D2%26hl%3Den%26sa%3DG&ei=l4GySsj3CNXf8Qb3mcGoDQ*

Higuchi, Y., et al., Three Staged Stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. Int J Radiat Oncol Biol Phys. 2009 Aug 1; 74(5): pp. 1543-1548.

SCREENING

20. Detection of Adenomas Found More Often in Morning Colonoscopies (Aug. 21/09)

The effectiveness of colonoscopy in preventing colon cancer depends on adenoma detection and removal. The adequacy of bowel preparation, careful mucosal visualization and adequate withdrawal time are known to affect adenoma detection rate (ADR). Physician fatigue, which usually increases as the day progresses, might impair ADR. The aim of this study was to assess the effect of timing of colonoscopy, morning vs. afternoon, on ADR. The results showed that doctors found more polyps (adenomas) when colonoscopies were done in the morning than in the afternoon. In the morning about 30 of every 100 patients had at least one polyp found during their colonoscopy. In the afternoon polyps were only found in 25 of every 100 patients. The adenoma detection rate tended to go down with each hour of the day. Whether or not this is due to physician fatigue or some other factor is not yet clear. Researchers recommend that the reasons and implications of this finding should be studied further.

Sanaka, Madhusudhan R., et al., Adenomas are detected more often in morning than in afternoon colonoscopy. The Amer J of Gastroenterology. 2009; 104: pp. 1659-1664

21. New Screening Test Developed to Detect Colorectal Cancers (Aug. 23/09)

A team of researchers from Japan and Dallas have developed a test to diagnose gastrointestinal cancers by analyzing the DNA fragments in human feces. The test relies on the fact that cancerous growths in the GI tract produce longer strands of DNA, and that those strands are more likely than other pieces of DNA to be sloughed out of the body via feces. The researchers identified 2 genetic biomarkers that were correlated with the severity of colorectal and gastric cancers. They then tested 303 stool samples from volunteers who were suspected of having colorectal tumors. Patients were instructed to collect equal fractional part (an aliquot) of feces using a paper spoon and to store it in a hermetically sealed plastic container. The container was then sealed in a Ziploc bag and stored overnight in the volunteer's refrigerator or freezer, then brought to a hospital the next day. The researchers were able to isolate the

key fragments of DNA and use them to diagnose cancers. But the test wasn't perfect for there were false positive and false negative results with the 2 markers. The researchers acknowledge that the test would be better with more reliable biomarkers. Overall, the screening test correctly identified 75% of people with colon cancer, 57% of those with stomach cancer and 44% of people with pre-cancerous growths in the colon (adenomas). While not perfect, the test did correctly detect three fourths of the colon cancers in this group of people. Not surprisingly, tweaking to improve its accuracy will be required.

Nagasaka, Takeshi, et al., Analysis of fecal DNA Methylation to Detect gastrointestinal neoplasia. J of the National Cancer Institute. Advance Access published online on August 21, 2009. DOI: 10.1093/jnci/djp265

OTHER

22. Bacteria-Causing Diarrhea May Cause Some Colon Cancers (Aug. 24/09)

Scientists from Johns Hopkins appear to have figured out how bacteria that cause diarrhea may also be the culprit in some colon cancers. The investigators say that strains of the common Bacteroides fragilis (ETBF) dupe immune system cells into permitting runaway colon tissue inflammation, a precursor for malignant growth. The study suggests that ETBF uses tissue inflammation to cause colon cancer in a similar way that the stomach bacteria H. pylori causes stomach tumors. A toxin-producing bacterium, the germ is widely known to cause diarrhea in children and adults in the developing and developed world, and a previous study in Turkey has linked it to colon cancer. The bacteria, which colonize in the gut, cause no symptoms in some individuals, but others develop diarrhea and colon inflammation, which has been linked to cancer growth. Unlike the case with H. pylori, it is unknown whether standard antibiotics can eradicate the microbe. To track the link between ETBF and colon cancer, the Johns Hopkins researchers conducted a series of tests in mice bred to carry mutations in a colon cancer-causing gene called APC. Their results show that mice infected with ETBF developed diarrhea which resolved quickly, but within a week, developed inflammation and small tumors in the colon. One month later, the colons were pockmarked with tumors. Researchers speculate that in humans, infection with ETBF produces a low-level inflammation that persists for a long time. If what we are seeing in mice holds true in humans, the chronic inflammation damages genetic material in the colon cells, allowing them to grow uncontrollably and develop into tumors earlier and more progressively than if they were not infected with ETBF. The microbe itself is difficult to culture from stool specimens, according to the investigators, so they are working on blood tests to detect antibodies to the pathogen's toxin, which may show whether an individual has been exposed to it and perhaps determine who may be at risk for colon cancer

Sears, Cynthia, et al., A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 cell responses. Nature Medicine. 2009: Vol. 15, pp. 1016-1022.

23. Risk of Developing Colorectal & Endometrial Cancers in Patients Who Have Genetic Mutation for Lynch Syndrome (Aug. 24/09)

Lynch syndrome, also called hereditary nonpolyposis colorectal cancer syndrome (HNPCC for short), is an inherited tendency to develop colorectal, endometrial (uterine) and other cancers. Inherited conditions are passed to an individual through their blood relatives. Although most cancers are not inherited, about 5% of people who have colorectal or endometrial cancer have Lynch syndrome. A new study estimates the lifetime risks for colorectal and endometrial cancer in people with a genetic mutation for Lynch syndrome. Even after adjusting for possible bias, a lifetime risk for both cancers was high and the need for special surveillance was critical. In 147 families with diagnosed Lynch syndrome (hereditary nonpolyposis colon cancer or HNPCC) there were 638 cases of colorectal cancer and 155 cases of endometrial cancer. All families had a mismatch repair (MMR) gene mutation (55 MLH1, 81 MSH2, and 11 MSH6). For men in the study:

- There was a 66% lifetime risk of colorectal cancer.
- Median age at diagnosis was 42.
- Highest lifetime risk was for men with an **MLH1 mutation**.

For women studied:

- There was a 43% risk of colorectal cancer.
- Median age at diagnosis of colorectal cancer was 47.
- Lifetime risk for endometrial cancer was 39%.
- Median age for endometrial cancer diagnosis was 47.5 years.
- Risk for either colorectal or endometrial cancer was 73%.

Researchers concluded lifetime risks of CRC and EC in mismatch repair gene mutation carriers are high. These estimates are valuable for patients and providers; specialized cancer surveillance is necessary.

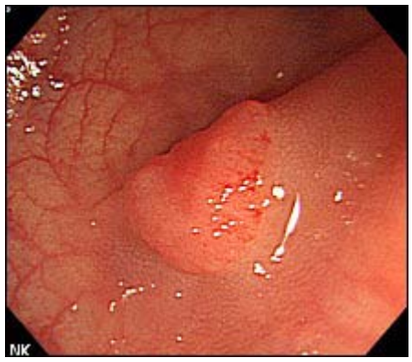
Another study in Canada that analyzed risk for colorectal cancer for families in Ontario with Lynch Syndrome found a 60% risk by age 70 for men and a 47% risk for women. Men who carried a MLH1 gene had a 67% risk, while women had a 35% risk. By age 90, risk of having colorectal cancer increased to 81% for men and 72% for women. Carriers of the MLH1 gene had a fairly consistent increase of risk over the general population over their lives. They were about 5 times more likely to get colorectal cancer at any age. However, relative risk decreased for MSH2 carriers. At age 30, they were thirteen times more likely to have cancer, decreasing to about 5% at age 70.

Stoffel, Elena, et al., Calculation of Risk of colorectal and endometrial cancer among patients with lynch syndrome. Gastroenterology. 2009: Published online ahead of print. DOI: 10.1053/j.gastro.2009.07.039

Choi, Yun-Hee, et al., Penetrance of colorectal cancer among MLH1/MSH2 carriers participating in the colorectal cancer familial registry in Ontario. Hereditary Cancer in Clinical Practice. 2009: Vol. 7, No. 14 DOI: 10.1186/1897-4287-7-14

24. Right-Sided Hyperplastic Colon Polyps Found to be Precursors to Adenomas (Aug. 25/09)

Serrated colorectal polyps (polyps having a jagged saw tooth appearance, hence their name "serrated," like a knife – see image below) include the following subgroups: **hyperplastic polyps**, **sessile (flat) serrated polyps** (also called sessile serrated adenomas), and **serrated adenomas**. Recent studies have found that serrated polyps share molecular qualities with a subgroup of colon cancers, leading to the hypothesis that serrated polyps can be precursors of cancer through a hyperplastic polyp to serrated adenoma to cancer sequence. These cancers tend to arise in the proximal colon (right sided colon). Sessile serrated polyps may be an intermediate step between hyperplastic polyp and serrated adenomas. There is currently very little understanding of the clinical significance of hyperplastic polyps and sessile serrated polyps to make reliable recommendations to clinicians about how to respond (e.g. when to repeat colonoscopy) when these lesions are detected. This study addresses this problem. The study material consisted of 40 consecutive polyps at least 5 mm in size from the proximal colon, identified in 2001 at a single institution, and interpreted as hyperplastic in 2001 by general pathologists. In 2007 reinterpretation was performed by 3 expert gastrointestinal pathologists, The gastrointestinal (GI) pathologists interpreted 85%, 43% and 30% of the polyps as sessile serrated polyps (sessile serrated adenomas). The results indicated that many polyps interpreted as hyperplastic in 2001 were considered sessile serrated lesions by GI pathologists in 2007, but there is substantial variation amongst GI pathologists. These results point to a problem for clinicians. Not only is the best clinical response to various types of serrated lesions uncertain, but the criteria for pathologic interpretation of these lesions and whether they can be reliably distinguished is still not fully established. Additional work is needed to clarify the pathologic interpretation of these lesions and define the clinical significance of subgroups of serrated colorectal polyps.



Serrated Polyp Located In The Sigmoid Colon

Source:
http://images.google.com/imgres?imgurl=http://www.omed.org/newsletter/200906/pic_art7_1.jpg&imgrefurl=http://www.omed.org/index.php/news_center/news_item/20090404/&usg=__6O_VQz_AZBfmg_E0KUfLbD9se14=&h=192&w=220&sz=14&hl=en&start=60&sig2=6b2li96UpLtylkpQresm1g&um=1&tbnid=TBz-9el2rgb_eM:&tbnh=93&tbnw=107&prev=/images%3Fq%3Dserrated%2Bpolyps%26ndsp%3D20%26hl%3Den%26sa%3DN%26start%3D40%26um%3D1&ei=Mla2SufFD6rK8QaKvszFDQ

Khalid et al., Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. World J of Gastroenterology, 2009; 15(30): pp. 3767. DOI: 10.3748/wjg.15.3767

25. Does Distance Affect Where Cancer Treatment & Care is Accessed? (Aug. 31/09)

Do patients choose where to get their care based on how long it takes for them to get there? Researchers have recently documented more patients seeking care at high volume centers, which are generally located in metropolitan areas. While trends like this should improve patient outcomes, this study shows that there are still a good number of patients who will not travel a long distance to get their care. Researchers are concerned that the long distances patients may need to travel will serve as a barrier to access to high volume centers. Centralization at high volume centers comes with a cost, as some patients may need to travel long distances to reach high volume centers. These increased travel distances may pose a significant barrier to quality cancer care for some patients. The study used discharge data from 1996-2006 for hospitals in New York, New Jersey and Pennsylvania. Patients ages 18 and over who were treated with surgery for colorectal, esophageal or pancreatic cancer were included. Over 272,000 procedures met criteria for inclusion in the study, specifically 5,273 esophageal,

13,472 pancreatic, 202,879 colon and 51,262 rectal procedures. A shift from low volume to high volume centers occurred to varying degrees for esophageal, pancreatic and colon cancer procedures. The change was the greatest for esophageal and pancreatic cancer, which are less common than cancers of the colon and rectum. Among the study population, travel distance increased for all patients, but more so for patients with less common cancers. For example, travel distance increased 72% for patients with esophageal cancer, compared to 17% for patients with colon cancer. The study demonstrated that the increase in travel distance was a direct result of the trend toward centralization at high volume centers. It also confirms what others have found, that disparities of cancer care exist. Since disadvantaged patients are more likely to remain at low volume centers, researchers worry that travel may increasingly serve as a barrier for these patients, especially during tough economic times.

Stitzenberg, Karyn B., et al., Centralization of Cancer surgery: implications for patient access to optimal care. J of Clin Oncology. Early Release, published online ahead of print Aug.31, 2009. DOI: 10.1200/JCO.2008.20.1715

26. Cancer Incidence & Outcome 10 Years After Mutation Testing for Lynch Syndrome (Sept. 3/09)

Colonoscopies with polypectomies (removal of polyps) and endometrial biopsies with transvaginal ultrasonography, repeated at 2- to 3-year intervals, are performed for prevention or early detection of cancer in patients with DNA mismatch repair gene mutation causing Lynch syndrome. This study evaluated the long-term effectiveness of surveillance in Lynch syndrome family members tested approximately 10 years ago. Cancer incidence and survival were determined after an 11.5 year follow up in 242 mutation positive and 367 mutation negative participants. Colorectal cancer occurred in 30 mutation positive participants and 74 participants had adenomas removed. 3 patients died of crc. Six of 112 women at risk had ovarian cancer. Cancer mortality rate and overall death rate were not significantly increased. Researchers concluded that long term compliance in surveillance for CRC exceeded 95% in Lynch syndrome. All crc deaths were not prevented as a result of noncompliance or missed lesions. Still, after 10 years of surveillance, no significant increase in mortality had occurred compared with mutation negative relatives.

Jarvinen, Heikki J., et al., Ten years after mutation testing for Lynch Syndrome: Cancer incidence and outcome in mutation-positive and mutation-negative family members. J of Clinical Oncology. JCO Early Release, published online ahead of print Aug.31, 2009. DOI: 10.1200/JCO.2009.23.7784

27. Colorectal Cancer Survival Affected by Spread into Nerves (Sept. 12/09)

According to this study, when cancer spreads to nerves near rectal and colon tumors, patients are four times as likely to die of cancer within five years of their diagnosis and twice as likely to experience a recurrence of stage II or III disease. *Perineural invasion* or PNI (spread of disease into nearby nerves) was found in about 1 out of every 5 colorectal cancers by a research team wishing to study this aspect of disease spread and associated outcome. In particular, stage II (node-negative) patients with PNI had significantly worse outcomes than even stage III patients without PNI. Although the researchers didn't have enough information to draw a firm conclusion, it appeared that those stage II patients with PNI who got chemotherapy after surgery did as well as stage II patients without PNI. PNI was more common as the cancer stage increased, with no cases in stage I and 57% in stage IV.

Liebig, Catherine, et al., Perineural Invasion is an independent predictor of outcome in colorectal cancer. J of Clinical Oncology. JCO Early Release, published online ahead of print Sept. 8, 2009. DOI: 10.1200/JCO.2009.22.4949

28. Kras Mutation & Aggressiveness of Hepatic Mets (Sept.13/09)

Observational studies of patients with primary colorectal cancer have identified KRAS mutation as a marker of poor prognosis. To examine more directly whether KRAS mutations are associated with accelerated metastatic progression, researchers from Sloan Ketterig evaluated KRAS mutation as well as Ki-67 expression in patients with colorectal liver metastases not treated with erbitux. Ki-67 is a tumour growth marker which can be readily detected and is present in the nuclei of growing cells. KRAS mutation status was assessed in a series of resected or sampled colorectal liver metastases. In a subset of these tumors, Ki-67 antigen expression was assessed. Median follow-up after liver resection or biopsy was 2.3 years. KRAS mutation in the liver metastasis was detected in 27% of the 188 patients. High Ki-67 expression in the liver metastasis was identified in 62% of 124 patients analyzed. Both markers were associated with multiple liver metastases and shorter time interval to their detection. KRAS mutation and high Ki-67 expression were predictors of poor survival after colon resection. Tumors with high Ki-67 expression were less likely to be selected for liver resection, and KRAS mutation was independently associated with poor survival after liver resection. Researchers concluded that **KRAS mutation is associated with more rapid and aggressive metastatic behavior of colorectal liver metastases**. These data suggest an important role for KRAS activation in colorectal cancer progression and advocate on behalf of continued efforts to develop KRAS pathway inhibitors for this disease.

Nash, GM, et al., Kras Mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. Ann Surg. Oncolo. 2009 Sept. 1. Epub ahead of print.

29. Addressing Cancer Pain (Sept. 14/09)

A new European study points to a disturbing problem among individuals with cancer: Under-treatment of cancer-related pain. Researchers conducted surveys in 11 countries across Europe plus Israel. They surveyed 5,049 people with cancer who reported having some pain at least once a week and discovered the following:

- 67% of patients reported that pain was "distressing"
- 56% suffered moderate-to-severe pain at least monthly
- 69% reported pain-related difficulties with everyday activities
- 50% felt that their quality of life was not a priority to their health care provider
- 12% felt that their provider did not understand that "pain is a problem"

While this research was not conducted in the United States or Canada, it is possible that similar problems may be occurring here as well. With proper attention to managing cancer-related pain, this unpleasant side effect of cancer care does not need to significantly affect one's quality of life. What should you do if you have pain from your cancer or its treatment?

□ **Don't suffer in silence**. Tell your doctor about any pain you experience right away. If you can't reach your doctor, call your nurse instead. He or she can get word to the doctor that a different pain management approach is needed.

□ **Don't skip doses**. If your doctor or nurse has given you a specific prescription for pain management, take your medication exactly as directed. Pain is much easier to prevent than to manage.

□ **Ask questions**. If there's something you don't understand about your cancer care, ask questions. Don't feel embarrassed about asking your health care provider to explain your medications to you a second time if needed.

□ **Write it down**. Take notes about each of your medications and how you are supposed to take them.

□ **Seek alternatives**. If you are taking a medication for pain management and it gives you side effects that are as unpleasant as, or even worse than, the pain, talk to your doctor about this. There are dozens of options for properly managing pain.

□ **Take a reality-check about addiction**. Many people fear that if they take any pain medication at all, they will end up addicted to it. If this is a concern, talk to your doctor about it. Learn how people are taken off pain medication when they no longer need it.

Ultimately, getting your pain managed properly rests with you. Being proactive about your cancer care, or asking a loved one to help you by calling the doctor to discuss your unmanaged pain will assist you in your desired goal of obtaining relief from pain.

Breivik, H., et al., Cancer-related pain: a pan-European survey of prevalence, treatment and patient attitudes. Annals of Oncology. 20(8): pp. 1420-1433.

30. Visceral Obesity (abdominal fat) & Insulin Resistance as Risk Factors for Colorectal Adenoma (Sept. 17/09)

Colorectal adenoma is known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue (VAT), or abdominal fat, measured by abdominal CT has not been documented clearly. In addition, the relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity and colorectal adenoma, has not been studied extensively either. The aim of this study was to examine VAT area and insulin resistance as risk factors of colorectal adenoma. A cross-sectional, case-control study was conducted in Koreans that presented for health check-ups. Patients underwent various laboratory tests, abdominal CT, and colonoscopy. According to the results, the prevalence of smoking, hypertension, metabolic syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and VAT areas were significantly different in the two groups. VAT area was independently associated with the risk of colorectal adenoma. Researchers concluded that visceral obesity was found to be an independent risk factor of colorectal adenoma, and insulin resistance was associated with the presence of colorectal adenoma.

NUTRITION & HEALTHY LIFESTYLE

31. Foods For Prevention and Recovery from Cancer (Aug. 19/09)

According to a new global policy report, it is estimated that 45% of colon cancer cases in the US are preventable through diet, physical activity and weight maintenance. The report also recommends policies to reduce the global number of cancer cases. There has been a lot of research in the field of cancer on foods that are beneficial in preventing and fighting cancer. The report summarizes its findings on preventing cancer through the following:

- Being as lean as possible without being underweight is one of the keys in preventing cancer. Try to hit the bottom range of the body mass index (BMI) for your height and age. Click here to determine your BMI as well as learning how to calculate your BMI.
- In addition to eating healthy, being physically active every day is another proven prevention tool. Aim for 30 minutes a day.
- Limit sugary drinks and processed foods (added sugar and fat, nutrients are stripped and are low in fiber).
- Basing your diet on fruits, vegetables and whole grains reduces cancer risk.
- Limit red meats and processed meats. Red meat contains substances that are linked to **colon cancer.**
- Limit alcoholic drinks. There is quite a bit of convincing evidence that alcohol increases the risk of cancer of the mouth, pharynx, larynx, esophagus, breast and colorectal.
- Limit salt consumption. Evidence shows a high probability between high salt consumption and stomach cancer.
- Aim to meet nutritional needs through diet alone, and moderate use of supplements.

http://www.aicr.org/site/News2?abbr=pr_&page=NewsArticle&id=14613&news_iv_ctrl=2461

32. Treating Constipation During Cancer Therapy (Aug. 20/09)

Diarrhea is not the only common gastrointestinal (GI) side effect during cancer care, but surprisingly, constipation can be more common. Some of the medications used to treat cancer and its side effects cause constipation. For this reason, constipation may result rendering the patient uncomfortable, sluggish and at times critical. If this is the case, there are many steps to alleviate constipation and re-establish regular bowel movements. The most important is to take medications as prescribed. If your medical team prescribes medication to ***prevent*** constipation, do not wait until you are constipated to take it. For some cancer treatments, taking anti-constipation medications before the problem develops is part of the plan. In addition to medical management, the following suggestions, which emanate from the American Dietetic Association, will help better manage constipation:

- It is helpful to know that physical activity can alleviate constipation. Even a short walk each day may help keep constipation at bay. Ask your doctor if it's OK for you to do some light activity, such as walking.
- Drink 8 to 10 cups of non-caffeinated fluids each day. Try water, juices, and caffeine-free tea. If you are losing weight due to treatment, stick to fluids with calories, such as juice, smoothies, and shakes.
- Drink warm liquids, such as soup or tea, especially first thing in the morning.
- Use high-liquid foods, such as popsicles and soup, to get fluid into your diet.
- Increase the fiber in your diet slowly. Try high-fiber foods such as fruit, vegetables, whole-grain breads and cereals, and beans and peas. If you have a lot of gas, skip the beans and peas for now.
- Snack on fiber-rich dried fruit, such as apricots, raisins, dried plums (prunes), and dates.
- Eat a breakfast that includes a warm drink and high-fiber foods, such as high-fiber cereal, oatmeal and whole grain toast.
- If you have a lot of gas, avoid carbonated drinks, broccoli, cabbage, cauliflower, dried beans, peas, onions, Brussels sprouts, Swiss chard, radishes, turnips, and watercress, all of which can cause more gas.
- Avoid straws and chewing gum, which can cause you to swallow air and feel even more bloated.

If you have constipation, **do not**:

- ☐ Use a lot of force or strain hard when trying to have a bowel movement.
- ☐ Use laxative medications unless your doctor or nurse tells you to use these products.
- ☐ Eat too many foods that can worsen constipation, including cheese and chocolate.
- ☐ Use enemas or laxatives if you have a low white blood cell count, unless your doctor tells you to do so.

You may wish to seek the advice of your physician if:

- ☐ It has been more than 2 days since your last bowel movement.
- ☐ Your constipation is accompanied by a fever.
- ☐ You see blood in your stool or in the toilet after a bowel movement.
- ☐ You have used a laxative (per your doctor's instructions) and you do not have a bowel movement within 36 hours.
- ☐ Your constipation is accompanied by persistent cramps, nausea, or vomiting.

Eds, Elliott L, et al., American Dietetic Association, Oncology Nutrition Dietetic Practice Group. The Clinical Guide to Oncology Nutrition, 2nd edition, 2008.

33. Website Providing Information on Omega-3s (Aug. 21/09)

Hoping to broaden understanding about the benefits of Omega-3 fatty acids, a Purdue University-based international consortium has launched a Web site and newsletter campaign to educate the public, physicians and veterinarians. Most people know that Omega-3 fatty acids are good for them and can often name a few foods that contain them, but the benefits extend far past this point. Omega 3s have been linked to improving state of health before, during and after a cancer diagnosis. People have heard of Omega-3s, but they don't understand what Omega-3s are, the types of Omega-3s in food and how to use them for better health. There are different types of Omega-3s needed throughout the lifetime. The website assists consumers with information that will help them make good decisions throughout their lives. Omega-3 fatty acids are found in nuts, oils and fish. Some are essential for retinal and brain development in infants, for instance, and for reducing the risk of cardiovascular disease in adults.

The Web site, http://www.omega3learning.purdue.edu, answers basic questions about what Omega-3 fatty acids do, where to find them and how to ensure a person is getting the right type of Omega-3s. There is also information for doctors and veterinarians, including fact sheets and handouts for their patients. There's a great deal of fundamental information for the consumers and doctors so they can better serve themselves and their patients. There also is a database of foods and pet-food products that contain Omega-3s, which includes the amounts and different types of Omega-3s found in each serving of a particular food, along with other dietary information. The site also includes a chart that shows how much and what type of Omega-3s men and women of different ages and with **differing health histories** should consume. Newsletters for doctors, veterinarians and consumers will go out every other month and can be received by signing up on the site.

http://www.omega3learning.purdue.edu

34. Vitamin D Improves Survival in Colorectal Cancer (Aug. 21/09)

Higher levels of vitamin D in the blood led to better survival after a colorectal cancer diagnosis. In the Nurses' Health Study and Health Professionals Follow Up Study, the 20% of patients with the highest levels of vitamin D in their blood after diagnosis had a 50% greater chance of not dying of colorectal cancer and a 38% better chance of being alive 5 years after their diagnosis. This study merely adds to the growing consensus that getting enough vitamin D is important not only for all, but especially for those with cancer. The study began in 1976 and it has collected information on a variety of health-related factors, such as diet and exercise habits, medications, and alcohol and tobacco use from approximately 238,000 female nurses. The health of each person in this study has been tracked over time to learn more about the potential causes of conditions such as cancer. For the purpose of studying the vitamin's effects on colorectal cancer, the researchers identified 1017 women who were diagnoses with colon cancer between 1986 and 2004. Researchers then studied the relationship between predicted vitamin D levels and survival after colon cancer. The results provide more evidence of vitamin D's importance to health and well being, even after a cancer diagnosis. The women with the highest predicted vitamin D levels had 50% lower risk of dying of colon cancer after diagnosis and 38% lower risk of dying of any cause. And finally, researchers did assert that taking vitamin D supplements to improve vitamin D levels in the body is safe for most people.

Ng, Kimmie, et al., Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. British J of Cancer. Advance online publication 18 August 2009. DOI: 10.1038/sj.bjc.6605262.

35. Tumours & Sugar Consumption (Aug. 22/09)

Researchers at Huntsman Cancer Institute (HCI) at the University of Utah have uncovered new information concerning the notion that sugar "feeds" tumors. It's been known since 1923 that tumor cells

use a lot more glucose than normal cells. The research helps show how this process takes place, and how it might be stopped to control tumor growth. During both normal and cancerous cell growth, a cellular process takes place that involves both glucose (sugar) and glutamine (an amino acid). Glucose and glutamine are both essential for cell growth, and it was long assumed they operated independently, but this research shows they are inter-dependent. Researchers discovered that by restricting glutamine availability, glucose utilization is also stopped. Essentially, if you don't have glutamine, the cell is short circuited due to a lack of glucose, which halts the growth of the tumor cell. The research focused on MondoA, a protein that is responsible for turning genes on and off. In the presence of glutamine, MondoA blocks the expression of a gene called TXNIP. This gene, TXNIP, is thought to be a tumor suppressor, but when it's blocked by MondoA , it allows cells to take up glucose, which in turn drives tumor growth. This study could lead to new drugs that would target glutamine utilization, or target MondoA or TXNIP. The next step in this research is to develop animal models to test the ideas about how MondoA and TXNIP control cell growth. If researchers come to understand that, they will then be in a position to break the cycle of glucose utilization which could be beneficial in the treatment of cancer.

Ayer, E., et al., Glutamine-dependent anapleurosis dictates glucose uptake and cell growth by regulating MondoA transcriptional activity. Proceedings of the National Academy of Science. Published online before print August 17, 2009. DOI: 10.1073/pnas.0901221106. Vol. 106 No. 35; pp. 14878-14883

36. Healthy Living is the Best Revenge for Cancer (Aug. 24/09)

In this study researchers describe how four key health behaviors can work together to greatly lower one's risk of diabetes, heart disease, stroke, and **cancer**. Apparently, the every day choices made - what to eat, whether or not to smoke, how much we move our bodies, and maintaining a healthy weight - can make all the difference in our long-term well being. The researchers collected information on diet, smoking and exercise habits, and body weight from 23,153, 35-to-65 year-old, German adults. They followed this group for approximately 8 years to see who developed diabetes or cancer, or had a heart attack or a stroke, during that time. Specifically, the study aimed to determine how the following factors affected disease risk:

- □ Never having smoked vs. currently or previously smoking
- □ Having a BMI (body mass index – see Item #31 for calculation) lower than 30 kilograms per meters squared (kg/m^2) vs. a BMI higher than 30 kg/m^2
- □ Getting at least 3.5 hours of physical activity per week vs. getting less than 3.5 hours of exercise weekly
- □ Eating a healthy diet, defined as eating plenty of fruits, vegetables, and whole-grain breads and eating only a small amount of meat, vs. eating a less-healthy diet

What researchers found was rather astonishing. Compared with people who practiced none of these behaviors, those who practiced all four had:

- 93% lower risk of developing diabetes
- 81% lower risk of having a heart attack
- 50% lower risk of having a stroke
- **36% lower risk of developing cancer**

For someone with a medical history that includes cancer, one of the potential downsides of reading about this type of research is the tendency to feel guilty or anxious about what you "should have, could have, would have" done differently to prevent cancer. While it may be natural to think this way, it is recommended that regrets be avoided as much as possible because there is never any definitive proof of what truly caused one's cancer. One positive way to put this information to good use in one's life is to know that it's never too late to eat healthfully, quit smoking and exercise regularly to improve health and help the body heal, recover, and stay well.

Ford, Earl S., et al., Healthy Living is the Best Revenge. Arch Intern Medicine. 2009; Vol. 169, Issue 15: pp. 1355-1362

37. Exercise Is Important Even After A Cancer Diagnosis (Aug. 24/09)

This study showed that elderly, overweight colorectal cancer survivors should adhere to a healthy lifestyle because lifestyle factors can significantly affect their quality of life. The study sought to determine whether overweight elderly cancer patients' quality of life -- long after their original diagnosis and treatment -- is affected by their health habits. To study this question, researchers interviewed 753 men and women, all at least 65 years old, who had survived 5 or more years after a breast, prostate, or **colorectal** cancer diagnosis. All were overweight to some degree, but none was morbidly obese. When the interviewers asked about exercise, diet, weight status, and quality of life, they found that half the group got no more than 10 minutes of moderate-to-vigorous exercise per week, and only 7% had healthful eating habits. Overall, the researchers report the survivors rated their mental and physical quality of life higher than average, compared to responses from age-matched normal populations. However, those who exercised more and had better diet quality also had better physical quality of life outcomes (e.g., better vitality and physical functioning) than those who exercised less and ate poorly.

Also, the greater the body weight, the poorer the physical quality of life was. In general, researchers concluded that the results point to "the potential negative impact of obesity and the positive impact of physical activity and a healthy diet on physical quality of life in cancer survivors". It's already known that physical activity is associated with a decreased risk of cancer recurrence and improved survival in both breast and colorectal cancer. Another reason to exercise is that older cancer survivors are at higher risk for functional decline - that is, the loss of their ability to perform their usual activities - compared to people of the same age who never had cancer. Also, researchers stated "there's some evidence that physical activity may help prevent sarcopenic obesity," a form of obesity associated with chemotherapy and hormonal therapy. "In terms of diet, it remains unclear whether following specific dietary guidelines improves outcomes in quality of life for specific cancers." Even so, researchers maintain that being overweight will worsen a variety of other medical conditions a cancer survivor might have.

Mosher, Catherine, et al., Associations between lifestyle factors and quality of life among older, long term breast, prostate, and colorectal cancer survivors. Cancer. Published online ahead of print. DOI: 10.1002/cncr.24436

38. Consumption of Fish and Risk of Colorectal Cancer (Aug. 31/09)

Evidence from lab and animal studies suggests that high fish consumption may reduce the risk of colorectal cancer, but the results of studies in humans have been inconsistent. The objective of this study was to prospectively examine the association between fish consumption and the risk of colorectal cancer incidence in Japan, where fish is widely consumed. Patients were between the age of 40-79 years old and free of cancer at the baseline. Fish consumption was assessed at the baseline using a self-administered food frequency questionnaire. Researchers found no connection between how much fish an individual eats and colorectal cancer. Following nearly 40,000 people for 9 years, the scientists found 566 cases of colorectal cancer but no difference in risk between those who ate the most fish and those who ate the least.

Sugawara, Y, et al., Fish consumption and the risk of colorectal cancer: the Ohsaki Cohort Study. British J of Cancer. (2009). Vol. 101, pp. 849-854.

39. Natural Agents May Partner With Chemotherapeutic Drugs To Treat Cancer (Aug. 31/09)

Research in the Linus Pauling Institute at Oregon State University suggests that some natural food compounds, which previously have been studied for their ability to prevent cancer, may be able to play a more significant role in treating it – working side-by-side with the conventional drugs that are now used in chemotherapy. Chlorophyllin is a water-soluble derivative of chlorophyll – the green pigment found in most plants and many food products that makes possible the process of photosynthesis and plant growth from the sun's energy. This study examined the activity of chlorophyllin and found that, on a dose-by-dose basis, it was 10 times more potent at causing death of colon cancer cells than hydroxyurea, a chemotherapeutic drug commonly used in cancer treatment. Beyond that, chlorophyllin kills cancer cells by blocking the same phase of cellular division that hydroxyurea does, but by a different mechanism. This suggests that it – and possibly other "cocktails" of natural products – might be developed to have a synergistic effect with conventional cancer drugs, helping them to work better or require less toxic dosages. Researchers found that chlorophyllin has the potential to be effective in the clinical setting, when used alone or in combination with currently available cancer therapeutic agents. The concept of combining conventional or new cancer drugs with natural compounds that have been shown to have anti-cancer properties is very promising. Most chemotherapeutic approaches to cancer try to target cancer cells specifically and do something that slows or stops their cell growth process. Researchers have now identified such mechanisms of action for natural compounds, including dietary agents. With further research researchers may be able to make the two approaches work together to enhance the effectiveness of cancer therapies. Chlorophyllin is inexpensive, and animal studies plus human clinical data suggest that it can be ingested at relatively high levels without toxicity. In this study, researchers found that pharmacologic doses of chlorophyllin caused colon cancer cells to spend more time than normal in their "synthesis phase" in which DNA is duplicated. Timing is critical to the various phases of cell growth, researchers said, and this disruption started a process that ultimately led to cell death. Further research is needed both in laboratory and animal studies, with combinations of chlorophyllin and existing cancer drugs, before it would be appropriate for human trials. Chlorophyllin, in general, is poorly absorbed from the human gastrointestinal tract, so it's unclear what levels might be needed for therapeutic purposes or how well they would work. Other dietary agents also might have similar potential. Work just published by LPI researchers in the journals Carcinogenesis and Cancer Prevention Research explored the role of organic selenium compounds in killing human prostate and colon cancer cells. In the recent studies, a form of organic selenium found naturally in garlic and Brazil nuts was converted in cancer cells to metabolites that acted as "HDAC inhibitors" – a promising field of research in which silenced tumor suppressor genes are re-activated, triggering cancer cell death.

Dashwood, Roderick, et al., E2F4 and ribonucleotide reductase mediate S-phase arrest in colon cancer cells treated with chlorophyllin. International J of Cancer. Vol 125, Issue 9, pp. 2086-2094

40. An All-Natural Multivitamin Decreases Colorectal Cancer Risk (Sept. 2/09)

A study printed in the American Journal of Epidemiology advocates on behalf of daily vitamin use. The research suggests that adults who take multivitamins for ten years or more have a substantially lower risk of developing colon cancer, when compared to those who do not. Their risk of developing colon cancer is apparently decreased by nearly 30% according to the results. Researchers maintain that the multivitamin selected should provide a broad spectrum of all natural vitamins and supplements that the body requires as well as having a long history of satisfied users.

http://allnaturalvitamins.wordpress.com/2009/08/31/take-an-all-natural-multivitamin-to-decrease-colorectal-cancer-risk

41. Diabetes Mellitus and Colorectal Cancer (Sept. 3/09)

Diabetes mellitus (sometimes called "sugar diabetes" or type II diabetes) is a condition that occurs when the body can't use glucose (a type of sugar) normally. Glucose is the main source of energy for the body's cells. The levels of glucose in the blood are controlled by a hormone called insulin, which is made by the pancreas. Insulin helps glucose enter the cells. In diabetes mellitus, the pancreas does not make enough insulin (type I diabetes)) or the body can't respond normally to the insulin that is made (type II diabetes). This causes glucose levels in the blood to rise. Diabetes mellitus increases the risk of incident colorectal cancer, but it is less clear if pre-existing diabetes mellitus influences mortality outcomes, recurrence risk, and/or treatment-related complications in colorectal cancer patients. This study performed a systematic review and meta-analysis (research compiled from many studies) comparing colorectal cancer mortality outcomes, cancer recurrence, and treatment-related complications in patients with and without diabetes mellitus. English studies that evaluated diabetes mellitus and cancer treatment outcomes, prognosis, and/or mortality were included. Researchers found significantly increased short-term perioperative mortality (death occurring around the time of surgery) in persons with diabetes mellitus. In the meta-analysis of long-term mortality, persons with diabetes mellitus had a 32% increase in mortality compared to those without diabetes mellitus. **The studies suggest that pre-existing diabetes mellitus predicts increased risk of some post-operative complications as well as 5-year cancer recurrence.** In contrast, there is little evidence that diabetes confers increased risk for long-term cancer-specific mortality. **Researchers concluded that patients with colorectal cancer and pre-existing diabetes mellitus have an increased risk of short- and long-term mortality.** They maintain that future research should determine whether improvements in prevention and treatment of diabetes mellitus will improve outcomes for colorectal cancer patients.

Stein, KB., et al., Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. Dig Diseases Sci. 2009 September 3; Epub ahead of print.

42. Lifestyle and Dietary Factors Can Prevent Colorectal Polyps (Sept. 3/09)

Not all polyps increase the risk of colon cancer, but a type called **serrated polyps** are considered "high risk" - meaning that if not found and removed, they can develop into cancer. New research points to some encouraging news: Our daily choices, including whether we smoke and what and how much we eat, can have a significant impact on our risk of developing these pre-cancerous, serrated polyps in the colon. We, therefore, have some personal control over our risk of developing colon cancer. The researchers from this study screened 2,830 adults two or more times for colon polyps during a 3-4 year period. They wanted to determine which lifestyle factors, such as tobacco use and eating habits, may be associated with developing serrated colon polyps. The following lifestyle factors were associated with increased risk of developing serrated polyps during the study:

- **Obesity**, which means having a body mass index (BMI) of 30 kilograms per meter squared (kg/m^2) or higher. A BMI of 30 kg/m^2 translates into being roughly 30 or more pounds over a healthy body weight.
- **Cigarette smoking**, not only increases the risk of colon cancer, but also cancers of the lung, head and neck, stomach, bladder, and pancreas.
- **Dietary fat**, with people who eat the most dietary fat having the highest risk of being diagnosed with serrated polyps.
- **Total Energy Intake**, which means that the people who eat the most calories have the highest risk of developing polyps. This ties in with the result that people who are obese have a higher risk of polyps: In general, people who eat the most calories are the most likely to be obese.
- **Red Meat Intake**, with people who eat the most red meat having the highest risk of developing serrated polyps. This finding is in agreement with much of the research on diet and colorectal cancer risk, including a recently released study (Internat J of Cancer, Vol 125, Issue 1, pp. 171-180) showing that both red meat and processed meat increase colorectal cancer risk. (See Item #43)
- **Folate supplements**, with people receiving folate treatment having a higher risk of polyps compared with people who do not use folate supplements. It's important to note that folate from foods, such as green leafy vegetables, appears to protect against colorectal cancer. Folate from supplements, on the other hand, appears to increase risk according to this study.

To put these research findings into practice, researchers recommend the following:

- Make a healthy body weight a priority in your life.
- If you smoke, quit as soon as you can.
- Cut back on the fat in your diet. Focus on cutting out some of the less healthy fats, which are found in processed foods such as chips, crackers, cookies, cakes, microwave meals, and fast food, and in fatty cuts of red meat. When you do eat fat, choose healthier fats such as nuts and seeds and olive and canola oil (for cooking).
- Eat less. More calories generally means more risk of many types of cancer, including colorectal cancer.
- Limit red meat to no more than 3 ounces per day, three to five days per week. You can substitute fish, chicken, beans, turkey, tofu, and other choices instead of red meat.
- Avoid folate supplements, unless you are pregnant, nursing, or advised by your doctor to take folate for some other medical condition. If you don't need folate for a specific reason, you should not supplement with this nutrient. Instead, get folate from food sources such as green leafy vegetables, orange juice, beans, lentils, and whole grains.

Wallace, Kristin, et al., The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prevention. 2009; Vol. 18, Issue 8: pp. 2310-2317

43. Drinking, Obesity and Smoking Raise Colorectal Cancer Risk (Sept. 3/09)

What we eat, how much we exercise, our use or avoidance of alcohol and tobacco, and whether or not we are obese or have diabetes all appear to play large roles in cancer risk, and this is especially true for colorectal cancer. Researchers have examined more than 100 studies on this topic to come up with an idea of just how strongly these factors are related to risk. A process called meta-analysis was used to combine and analyze data from 103 previous studies. The advantage of this approach is that it allows for large numbers of people to be studied together. The more people in a study, the more likely it is that relationships between causes and effects will be discovered, if they exist. The study revealed the following:

- Heavy drinkers had 56% higher risk of colorectal cancer compared with light and nondrinkers.
- Smokers had 16% greater risk of colorectal cancer than people who never smoked.
- People consuming the most red and processed meat had approximately a 20% higher risk of colorectal cancer than people consuming the least of these foods.
- People classified as obese—having a body mass index (BMI) of 30 kilograms per meter squared (kg/m2) or higher (in other words, being roughly 30 or more pounds over a healthy body weight), had 40% higher risk of colorectal cancer compared with people with a BMI of 25 kg/m2 or less (considered to signal a healthy body weight).
- People who were the most physically active had 20% lower risk of colorectal cancer compared with people getting the least physical activity.
- People with diabetes had a 23% higher risk of developing colorectal cancer as compared with people without diabetes.

This study supports what many health experts have long known: Of all cancer types, cancers of the colon and rectum are among the most strongly related to everyday health choices. The following are recommended:

- Drink alcohol only in moderation or not at all. This means no more than two drinks per day for men and one drink per day for women, with a drink measuring 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor.
- If you smoke, quit. Limit red and processed meat to no more than 3 ounces per day, three to five days per week. Try fish, chicken, beans, tofu, and other choices instead of meat.
- Make regular physical activity a part of your day and focus on keeping your body weight in a healthy range. Both of these actions will help you avoid diabetes, and if you already have this disease, keep it under good control.

Woodward, Mark, et al., The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. International J of Cancer. Vol. 125, Issue 1, pp. 171-180