

COLORECTAL CANCER RESEARCH
Week Ending August 22, 2008

The following colorectal cancer research update extends from August 9 – August 22, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. Avastin May Not Show Therapeutic Benefit in C-08 Trial for Adjuvant Colorectal Cancer (Stage III Patients)??? (Aug 20/08)

An ongoing trial NSABP C-08 is studying the effect of the combination of Avastin and folfox on prolonging disease free survival and overall survival on stage III colorectal cancer patients. Some physicians are questioning avastin's therapeutic benefit in this current trial. After a stage III crc patient has had surgery, patients do not have rooted tumors, however, they might have tumors circulating in their blood stream which are approximately 100 to 1000 cells in size. Some physicians believe that giving patients avastin could potentially keep these tumors from finding solid ground and growing as a result of avastin's anti-angiogenic properties - the prevention of the development of new blood vessels - which could potentially supply the tumor with nutrients needed to proliferate. Yet circulating tumor cells in the adjuvant setting could also possibly derive the nutrients needed to grow and thrive through diffusion, according to some physicians. If this is the case, then the cancer might still survive and grow. Though other physicians have commented that if one of these micrometastases landed in an organ and set up root, avastin could prevent the micrometastases from taking root, though no one is certain of that fact. Results of the ongoing trials need to become available before any conclusions can be drawn.
<http://www.nsabp.pitt.edu/C-08.asp>

www.ft.com/cms/s/2/9de29d56-6ead-11dd-a80a-0000779fd18c.dwp_uuid=e8477cc

2. Efficacy of Adjuvant Chemo with 5FU in CRC Depends on the Mismatch Repair Status (Aug 22/08)

The aim of this study was to evaluate if mismatch repair (MMR) status (genetic deficiency) had a different response to adjuvant (post surgical) 5FU chemotherapy in Stage II and III colorectal cancer patients who were followed during 5 years. MMR deficiency was found in 76 (10.1%) colorectal cancer patients. No differences were found in overall survival or disease-free survival regarding MMR status. Adjuvant chemo improves survival in patients in stage II or III, but this improvement is only evident in patients with MMR-competent tumours. Survival of patients with MMR-defective tumours does not improve with adjuvant chemo. There appeared to be an independent effect of the interaction between MMR status and adjuvant chemo. Investigators concluded that in colorectal cancer patients, those with MMR deficient tumours seemed not to benefit from 5FU based chemo.

Rodrigo Jover, et al., The Efficacy of Adjuvant Chemotherapy with 5-Fluorouracil in Colorectal Cancer Depends on the Mismatch Repair Status, European Journal of Cancer, Aug 22, 2008; Online Edition.

SURGERY

3. Chewing Gum Relieves Ileus After Colorectal Surgery (Aug 18/08)

Gum chewing may kick start bowel function after colectomy and possibly reduce hospital stay as well, according to a meta-analysis. Patients who chewed gum after surgery passed flatus a mean of 0.66 days more quickly than those who did not chew gum and had their first bowel movement 1.10 days more quickly, reported Paris P. Tekkis, M.D. of St. Mary's Hospital and colleagues in the Archives of Surgery. Length of hospital stay tended to fall by more than a day for gum chewers compared with controls. Gum chewing acts as "sham feeding" to produce saliva and pancreatic secretions and is thought to trigger gastrointestinal hormone release and cephalic-vagal stimulation, according to the investigators. Patients chewed sugarless gum for a period ranging from 5 to 45 minutes 3 times a day after surgery. All five studies included control groups with identical perioperative treatment aside from chewing gum. The benefits included:

- Significantly shorter time to pass flatus
- Significantly shorter time to first bowel movement
- A trend toward reduced postoperative length of hospital stay

Purkayasha S, et al., Meta-analysis of Randomized Studies Evaluating Chewing Gum to Enhance Postoperative Recovery Following Colectomy, Arch Surg 2008; 143: 788-793

4. Should Patients with CRC and Nonresectable Liver Mets Have Bowel Surgery? (Aug 9/08)

In a nonrandomized trial, 42 patients with stage IV crc and unresectable liver mets were initially treated with resection of the primary tumor plus chemotherapy. The results were compared with those from 23 similar patients who were initially treated with only chemotherapy. Survival was significantly improved in the group receiving initial surgical therapy (26 months) compared to a mean survival of 16.9 months in the group initially receiving chemotherapy. Hence, patients who selected initially surgical removal of the primary tumor had improved survival rates. Shrinkage of the liver tumors also occurred in some patients after receiving chemotherapy, allowing for eventual excision. A US randomized clinical trial (NSABP C-10) that is designed to determine the best treatment for crc is now under way.

Galizia, G, et al., First line chemotherapy vs. bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Arch Surg. 2008; 143(4):352-8

5. Is Hepatic Resection Justified After Chemotherapy in Patients With Colorectal Liver Mets and Lymph Node Involvement? (Aug 20/08)

For patients with colorectal liver mets, regional lymph node involvement can be problematic in terms of overall survival. This study sought to evaluate the ability of a multidisciplinary approach, including preoperative chemo and liver resectioning, to improve patient outcomes. Patients were treated as having colorectal cancer liver mets and simultaneous regional lymph node involvement and then compared to patients without regional lymph node involvement. Investigators concluded that combined liver resection and pedicular lymphadenectomy is justified when regional lymph node mets respond to or are stabilized by preoperative chemo.

Adam, Rene, et al., Is Hepatic Resection Justified After Chemotherapy in Patients With Colorectal Liver Metastases and Lymph Node Involvement? J Clin Oncology, August 1, 2008; 26(22): 3663-3664

6. Patterns of Recurrence Following Liver Resection for Colorectal Mets (Aug 21/08)

Patients with rectal cancer are at increased risk of local regional recurrence compared with patients with colon cancer. This may affect the pattern of recurrence and survival rates following hepatic resection of liver mets from rectal cancer. From April 1, 1984 to December 31, 2005, 582 patients with liver mets from a primary colorectal adenocarcinoma underwent liver resection and the results were analyzed. Following resection of hepatic rectal mets, pelvic recurrence is relatively common, and most patients with pelvic recurrence will also develop recurrence in the liver. **Surgery for recurrent disease following hepatic resection of rectal mets is warranted among well-selected patients for it appears to promote the greatest outcomes for patients.**

Assumpcao, Lia, et al., Patterns of Recurrence Following Liver Resection for Colorectal Metastases, Arch Surg, 2008; 143(8): 743-749

7. Quality of Life & Patient's Expectations after Closure of a Temporary Stoma (Aug 10/08)

Little is known about the changes in quality of life following reversal of a temporary loop ileostomy after rectal cancer surgery. A study was dedicated to assessing physical symptoms, quality of life, problems in everyday life, and patient's expectations and complaints. The interviews showed a significant improvement in body image and leisure activities while the questionnaires showed no change in quality of life. Conversely, there was a significant increase in G.I. problems that persisted until 1 year after primary surgery. An increasing proportion of patients stated that they felt worse than they expected after stoma closure. And that was accompanied by an increased number of complaints about the hospital and medical staff. Although from the surgeon's point of view, stoma closure is only a minor procedure, it causes significant functional problems for the patients that lead to considerable dissatisfaction. Other than usually presupposed, there is no general improvement in quality of life and everyday life after stoma closure. Therefore, thorough preoperative counseling about the consequences of stoma reversal is mandatory.

Siassi, Michael, et al., Quality of Life and Patient's Expectations After Closure of a Temporary Stoma, International Journal of Colorectal Disease, Aug 2008, Online Publication, 1432-1262.

RADIATION

8. Radiofrequency Ablation Effective for Primary Lung Tumors and Lung Mets from Colon Cancer (Aug 21/08)

The use of radiofrequency ablation for the treatment of lung cancer and lung mets from colon cancer is effective and safe for some patients. These results were recently published in the Lancet Oncology. RFA is commonly used for the treatment of tumors in the liver that are not amenable to surgery. The procedure involves the use of a small probe inserted into the site of cancer. The physician guides the probe through scans so that the treatment can be contained within the site of cancer, limiting the impact on surrounding tissue. Radio waves flow through the probe to the site of cancer, thereby destroying the cells. RFA typically requires local anesthesia, no surgery and affects only the site of cancer without causing side effects to the rest of the body. Researchers from Europe, the US and Australia recently conducted a clinical trial, referred to as the RAPTURE study, to further evaluate the use of RFA in lung tumors among 106 patients. Patients had either lung cancer or mets to the lungs originating from colon cancer measuring 3.5 cm or smaller. Patients underwent RFA and were followed for 2 years. Overall survival for patients who had colon cancer mets to the lungs at 1 year was 89% and at the 2 year mark was 66%. The researchers concluded that RFA appears to be a promising treatment for patients with either primary or metastatic lung cancer who are not suitable candidates for other treatment alternatives.

Lencioni R, et al., Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study. Lancet Oncology. 2008; 9:621-628

OTHER

9. Call for New Staging System for Advanced Colorectal Cancer

Experts in treating colorectal cancer that has spread to distant sites say that the need for a better staging system for advanced disease is urgent. More specific staging could identify patients whose cancer could be cured with surgery. For others, modern chemotherapy might make curative surgery possible. In addition, a more precise staging system, with more categories, would provide better survival prognosis. Currently, all patients whose cancer has spread beyond their colon or rectum to distant sites are lumped together in one group, classified as stage IV or Dukes D. No difference is made for those who have liver tumors that could be surgically removed or those where chemo might make a surgical cure possible. Better chemo and improved surgical techniques have increased the percentage of patients with potentially curable colorectal cancer, but staging doesn't reflect those improvements. Surgeons no longer count the number of liver tumors to decide whether or not a patient can be helped surgically. Instead they look at whether they can remove all signs of cancer and leave 20-30% of healthy liver to re-grow after the operation. They also consider if the patient is healthy enough for surgery and whether cancer is limited to the liver or is more widespread in the body. Previously surgeons were unwilling to operate if there were any additional metastatic tumors outside the liver, but new approaches have changed that. If cancer outside the liver can also be completely removed surgically, then the liver tumours are considered resectable. The researchers conclude that the current staging system for advanced crc is flawed and out of date and does not reflect current treatment strategies or prognoses for patients with mcrc.

Poston et al., Journal of Clinical Oncology, published early online, August 18, 1008

10. Depression Can Hasten Cancer Death (Aug 10/08)

Depressed patients with advanced cancer die sooner than those who are not depressed. The more serious the depression the more likely they are to die prematurely. Researchers in the United Kingdom screened cancer patients for depression using tests that were originally designed to diagnose depression in women after childbirth. They looked at feelings of worthlessness and sadness and thoughts of suicide, as well as measuring pain and cancer symptoms. They found a little less than one-third of advanced cancer patients were depressed. Six months later half of those identified patients who were still alive remained depressed. In addition to depression, symptoms of tiredness and breathlessness were also associated with a risk of earlier death. Lead investigator asserts that even those cancer patients who are very ill can still be effectively treated for depression but the first step in the treatment is the recognition that the patient is depressed.

www.omega3healing.com/omega-3-and-cancer

11. Stem Cell Marker Gives New Clue to Bowel Cancer (Aug 20/08)

A new test could predict those at risk of the most aggressive and deadly form of bowel cancer, boosting survival rates. A British team has come up with a new insight into how to spot who has a more dangerous form of the disease that should be treated with chemotherapy and not just surgery to remove the growth. They studied tissue samples from 700 crc patients and tracked their progress. The team focused on stem cells, the parent cells of other types and found that **lamin A** marked them out. Cancer cells had this property too. They found that patients with tumour tissue which also carried lamin A were more likely to have an aggressive form of the disease. Lamin A plays a role in reducing cell adhesion so the cancer can more easily spread and invade the rest of the body. If the lamin A marker is detected in the early forms of the cancer, these patients should be given chemo in addition to the usual surgery, when the tumor and some surrounding tissue is removed, so as to prolong overall survival.

www.telegraph.co.uk/core/Content/display

12. Discovery of Major Genetic Cause of Colorectal Cancer (Aug 14/08)

Scientists at Northwestern University's Feinberg School of Medicine and colleagues have discovered a genetic trait that is present in 10 – 20% of patients with colorectal cancer. The findings strongly suggest that the trait is a major contributor to crc risk and likely the most common cause of crc to date. If a person inherits this trait – which is dominant and clusters in families – the study found the lifetime risk of developing crc is 50%, compared to 6% for the general population. The trait, which has been named **TGFBR1 ASE**, results in decreased production of a key receptor for TGF-beta, the most potent inhibitor of cell growth. With less of this vital protective substance to inhibit cell growth, colon cancer can more easily develop. The results of this study show that decreased production of this receptor for TGF-beta was present in 10-20% of patients with crc. Decreased production of the same receptor was present in only 1-3% in healthy control groups.

www.northwestern.edu/

NUTRITION

13. More Fruits & Vegetables, Less Meat Reduces Colorectal Cancer (Aug 14/08)

Individuals who consume a diet that is rich in vegetables, fruits, whole grains, and healthy oils, contains sufficient dietary calcium and vitamin D, and is low in solid fats, added sugar, and red meats have a significantly reduced risk of developing colorectal cancer. These results were recently published in the American Journal of Epidemiology. Evidence continues to mount indicating that a patient's lifestyle habits, including diet, may significantly decrease the risk of certain types of disease, including certain types of cancers. Specifically, increased consumption of fruits, vegetables, and whole grains with a reduction in red or grilled meats appears to reduce the risk of colorectal cancer. Researchers affiliated with the National Cancer Institute recently conducted a clinical study to further evaluate the potential associations between diet and rates of colorectal cancer among individuals involved in the NIH-AARP Diet and Health Study. The study included approximately 500,000 individuals who completed questionnaires regarding their dietary habits. Overall, individuals who ate more fruits, vegetables, healthy fats, and whole grains while minimizing consumption of red meat, added sugars, and oils had a significantly reduced risk of developing crc.

Reedy J, et al., Index-based dietary patterns and risk of colorectal cancer. American Journal of Epidemiology. 2008; 168:38-48

14. High BMI Increases Risk of Colorectal Adenomas (Aug 20/08)

A scientific study in the August issue of the American Journal of Gastroenterology examines the association between obesity and the risk of colorectal adenomas. Researchers at the University of Tokyo examined the effect of body weight on the incidence of colorectal adenoma in 7,963 Japanese patients who underwent colonoscopy between 1991 and 2003. Researchers found 20.7% of patients had at least 1 colorectal adenoma. It is important to note that as BMI increased, so did the prevalence of colorectal adenomas. In a separate cohort analysis, 2,568 patients from the initial study underwent a second colonoscopy after 1 year to compare the effect of body weight changes on the development of new colorectal adenomas. The incidence rates of colorectal adenoma were 9.3% in patients who lost 5% or more in body weight, 16.2% in

patients who gained 5% or more in body weight, and 17.1% in patients who neither gained nor lost weight. Weight loss was associated with lowered incidence of adenoma, independent of gender, age, initial colonoscopic findings and initial BMI. Based on their findings, the authors suggest that *controlling body weight may decrease the risk of developing colorectal adenomas*.

Calculating BMI:
$$\text{BMI} = 703 \times \frac{\text{Weight (lbs)}}{\text{Height}^2 \text{ (in)}}$$

If BMI is less than 18.5, it is indicative of being underweight.
If BMI is greater than 25, it is indicative of being overweight.
If BMI is over 30, considered obese.

BMI Prime is a simple modification of BMI System. It is the ratio of actual BMI to upper limit BMI which is 25.

ie. If your BMI = 34, then BMI Prime = $34/25 = 1.36$ BMI Prime -> **36%** over upper mass limit.

If BMI Prime is **0.74 or less**, considered underweight;
If BMI Prime is **0.75 – 0.99**, optimal weight;
If BMI Prime is **1 or greater**, considered overweight.

www.sciencedaily.com

15. Vitamin D helps Colorectal Cancer Patients: Study (Aug 20/08)

Vitamin D may extend the lives of people with colon and rectal cancer, according to a study published in the Journal of Clinical Oncology suggesting another health benefit from the sunshine vitamin. Previous research has indicated that people with higher levels of vitamin D may be less likely to develop colon and rectal cancer. The new study led by Dr. Kimmie Ng of the Dana-Farber Cancer Institute in Boston involved 304 men and women diagnosed with colorectal cancer from 1991 to 2002, to see if higher levels of vitamin D in the patients affected their survival changes. In fact that turned out to be the case. The researchers used blood samples to determine vitamin D levels of the patients, and they were tracked for an average of about 6.5 years. Those in the highest 25 percent of vitamin D levels were about 50 percent less likely to die during the study from their cancer or any other cause compared to the patients in the lowest 25 percent of vitamin D levels. Ng said a clinical study is being planned to test vitamin D as part of colorectal cancer treatment. It would involve patients who already have gotten their cancer surgically removed, with some getting chemotherapy with vitamin D after surgery and the others getting just the standard chemo.

Ng Kimmie, et al., circulating 25-Hydroxyvitamin D Levels and Survival in Patients with Colorectal cancer, Journal of Clinical Oncology, Vol 26, No 18, 2008; 2984-2991