

COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH

Week Ending October 3, 2008

The following colorectal cancer research update extends from September 20 – October 3, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. Erbitux Offers “cure” Potential To 3 Out of 4 Advanced Colon Cancer Patients - But Conditions Apply (Sept 20/08)

Researchers have narrowed down the conditions in metastatic colorectal cancer where treatment with the targeted biologic therapy erbitux is most likely to succeed. Results from 2 studies (CRYSTAL & CELIM) presented at the European Society for Medical Oncology congress in Stockholm, Sweden, showed that patients with a specific but common genetic make-up in their tumours, and whose mets were limited to the liver, have a greater than 75% chance of going on to potentially curative surgery. If those liver metastases respond well to therapy, they can then be removed surgically, and if excised completely, that patient is technically cured, provided the cancer does not recur. Patients, whose tumours tested positive for the Kras wild type gene, demonstrated a good response to erbitux and chemo in the studies. However, those patients whose tumours tested positive to the mutated version of the Kras gene did not respond well to the added component of erbitux with their chemo regimen.

www.medicalnewstoday.com

2. Elderly Patients With Metastatic Colorectal Cancer Can Safely Be Treated With Standard Chemotherapy Regimens (Sept 21/08)

According to a Phase III study published in the Oncology Times, elderly patients with metastatic colorectal cancer can safely be treated with standard chemotherapy regimens. In a study of 142 patients age 75 and older given 5FU based chemo with or without irinotecan, 54 patients suffered serious adverse events. Only 2 of them died from treatment toxicities – one in each arm. Studies such as this are important for several reasons, according to the lead investigator. First, half of all cancers occur in patients age 70 and older. Also, elderly patients without cancer live a long time. Eighty-year olds from Western nations can expect to have almost a decade of life ahead of them. Despite these facts, the elderly are under represented in clinical trials, due either to exclusion or low enrollment numbers even if allowed. Despite our perception, two-thirds of patients aged 70 to 95 are willing to undergo high-intensity chemotherapy if offered and almost all would take ‘mild’ chemotherapy. The prospective study confirms that we should not exclude a large group of patients from getting chemo because of a nonspecific selective criterion of age.

Mitry, E, et al., Elderly Patients With Metastatic Colorectal Cancer Can Safely Be Treated With Standard Chemotherapy Regimens. Oncology Times: Volume 30(17)10 September 2008 p24

3. Capecitabine Plus Oxaliplatin (Xelox) vs 5FU/folinic acid Plus Oxaliplatin (folfox-4) as Second Line Therapy in Metastatic Colorectal Cancer: a Randomized Phase III Noninferiority Study (Sept.24/08)

Multi-centre studies demonstrated the noninferiority of capecitabine plus oxaliplatin (Xelox) vs. 5FU/folinic acid and oxaliplatin (folfox4) as second line therapy in patients with metastatic colorectal cancer after prior irinotecan-based chemotherapy. A total of 627 patients were randomly assigned to receive Xelox or folfox 4 following disease progression/recurrence or intolerance to irinotecan based chemotherapy. The primary end point was progression free survival. Progression free survival for Xelox (4.7 months) was noninferior to folfox4 (4.8 months) and overall survival was 11.9 months vs. 12.5 months respectively. The lead investigator concluded that Xelox is noninferior to folfox4 when administered as second-line treatment in patients with mcr.

Rothenberg, M. et al., Capecitabine plus oxaliplatin vs 5fluorouracil/folinic acid plus oxaliplatin (folfox4) as second line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Annals of Oncology. Vol 19, N 10. 2008 pp 1720-1726.

4. Health-Related Quality of Life Impact of Bevacizumab (Avastin) when Combined with Irinotecan, 5FU, and Leucovorin or 5FU and Leucovorin for Metastatic Colorectal Cancer (Sept. 29/08)

The time to deterioration in health-related quality of life was compared in patients with previously untreated metastatic colorectal cancer receiving a 5FU-based chemo regimen with or without the addition of avastin in 2 randomized, placebo-controlled studies. 127 patients received irinotecan, 5FU and leucovorin and 122 patients received irinotecan, 5FU, leucovorin plus avastin. The time to deterioration in health-related quality of life did not differ significantly between treatment groups as measured by the assessment indices and total scores. However, the conclusions of the lead investigators are as follows: **When added to 5FU chemo, avastin significantly prolonged overall survival and progression free survival without compromising health related quality of life.**

Kabbinavar, F, et al., Health-Related Quality of Life Impact of Bevacizumab When Combined With Irinotecan, 5Fluorouracil, and Leucovorin or 5Fluorouracil and Leucovorin for Metastatic Colorectal Cancer. The Oncologist. Vol 13, No 9 Sept 2008. 1021-1029

5. Oxaliplatin Plus Irinotecan Compared With Irinotecan Alone As Second Line Treatment After Single Agent Fluoropyrimidine Therapy for Metastatic Colorectal Carcinoma (Oct. 1/08)

A study appears to conclude that irinotecan plus oxaliplatin (irox) is superior to irinotecan alone in patients with mcrC previously treated with single-agent fluoropyrimidines (ie 5FU). A phase III, randomized, open-label, multicenter study of patients with metastatic or recurrent crC that had progressed or recurred during or after adjuvant or first line fluoropyrimidines (fluorouracil/leucovorin or capecitabine, the latter only for metastatic crC). Patients received irox or irinotecan alone every 3 weeks. Overall survival was 13.4 months for the irox group and 11.1 months for the irinotecan group. Overall response rate was 22% vs. 7% respectively and time to progression was 5.3 months vs. 2.8 months respectively. Investigators concluded that Irox is an effective treatment for mcrC that has progressed after first line fluoropyrimidine therapy. Irox improves efficacy compared with irinotecan alone, providing an additional option in the postadjuvant or second line treatment setting for patients who experience treatment failure with single agent fluoropyrimidine therapy.

Haller, D, et al., Oxaliplatin Plus Irinotecan Compared with Irinotecan Alone as Second Line Treatment After Single-Agent Fluoropyrimidine Therapy for Metastatic Colorectal Carcinoma. Journal Of Clinical Oncology, Bol 26 No 28 October 1, 2008 p 4544-4550

6. Immunotherapy for Metastatic Colorectal Cancer (Jul 08)

A startling report by Dr. Yamamoto and colleagues (director of the Division of Cancer Immunology and Molecular Biology, Socrates Institute for Therapeutic Immunology, Philadelphia, Penn), published in the July issue of Cancer Immunology Immunotherapy, highlights the remarkable results of Gc-MAF therapy which totally abolished tumors in 8 colon cancer patients who had already undergone surgery but still exhibited circulating cancer cells (mets). After 32-50 weekly injections, all crC patients exhibited healthy control levels, indicating eradication of metastatic tumour cells, an effect that lasted 7 years with no indication of cancer recurrence either by enzyme activity (nagalase) or CT scans.

The weekly injection of just 100 billionths of a gram of a harmless glyco-protein (a naturally produced molecule with a sugar component and a protein component) activates the human immune system and appears to "cure" cancer for good, according to human studies among breast cancer and colon cancer patients, producing complete remissions lasting 4 and 7 years respectively. This glyco-protein is thus far without side effects. Normal Gc protein (also called vitamin D binding protein), an abundant glyco-protein found in human blood serum, activates macrophages (a type of white blood cell that ingests and destroys tumour cells) when it is converted to its active form, called Gc macrophage activating factor (**Gc MAF**). Gc protein is converted to **Gc-MAF** with the help of B and T cells. Unfortunately, cancer cells prevent the conversion of Gc protein to **Gc-MAF** by secreting an enzyme known as Nagalase, which prevents **Gc-MAF** from destroying tumour cells. This is the way cancer cells escape detection and destruction, by disengaging the human immune system. The once-weekly injection of minute amounts of **Gc-MAF**, just 100 nanograms activates macrophages and allows the immune system to pursue cancer cells with vigor, sufficient to produce total long-term remissions in humans.

Yamamoto, N, et al., Immunotherapy of metastatic colorectal cancer with vitamin D-binding protein-derived macrophage-activating factor, GcMAF. Cancer Immunology, Immunotherapy, Vol 57, No 7, July 2008, pp 1007-1016

www.waccobb.net/forums/showthread.php?t=37661

SURGICAL

7. Is Local Anesthetic Wound Infusion Following Laparotomy Effective For Colorectal Surgery? (Sept. 22/08)

A review published in World Journal of Gastroenterology brings light to the fact that many multimodal regimens for analgesia following major colorectal laparotomy provide inadequate pain relief. Continuous wound infusions of local anaesthetics are a promising development as an adjunct to existing multimodal postoperative analgesic regimens and the article provides a quantitative review of the evidence specific to colorectal laparotomy. The review highlights the potential benefit of continuous wound infusions of local anaesthetics in terms of reduction in opioid consumption following laparotomy for major crc surgery and the need for future research on this topic.

Karthikesalingam A, et al., Continuous Wound Infusion of Local anaesthetic Agents Following Colorectal Surgery: Systematic Review and Meta-Analysis. World J Gastroenterology 2008; 14(34): 5301-5305

8. Quality of Colon Cancer Surgery Determines Patient Survival (Sept 24/08)

A research study has suggested for the first time that the quality of surgery for colon cancer is associated with patient survival. UK researchers found marked variability in the plane of surgery (the directions in which dissection is carried out) in operations to remove colon cancers, with direct impact on survival, when they analyzed the tissue removed during cancer surgery in nearly 400 patients. Previous studies have shown that the quality of rectal cancer surgery improves patient outcomes and total mesorectal excision (TME) for rectal cancer has now become the standard surgical procedure for this cancer type. The researchers in this study wanted to see whether the quality of colon cancer surgery could have a similar effect on patient outcomes. They decided to examine whether the removal of an intact colonic mesentery (the folds of peritoneum that attach the colon to the back wall of the abdomen), might minimize the risk of cancer spread and survival results showed that patients undergoing mesocolic plane surgery had a 15% overall survival advantage at 5 years when compared with those who had surgery in the muscularis propria plane.

West, NP, et al., Pathology Grading of Colon Cancer Surgical Resection and Its Association with Survival: A retrospective Observational Study. Lancet Oncology 2008; 9: 857-865

9. Surgical Treatment Provides New Option for Some Colorectal Cancer Patients (Sept. 30/08)

Research out of Wake Forest University School of Medicine suggests that a surgical technique not traditionally used in advanced abdominal cancer may be a viable treatment option for some patients previously thought to be untreatable, offering the real possibility of extending survival for those patients. The study, is the first to compare the success of techniques used to remove liver cancers to the effectiveness of those same techniques in removing cancers from the abdominal wall (peritoneum). Peritoneal surface disease (PSD) appearing from the spread of colon cancer has not traditionally been considered treatable with surgery because of the difficulty of finding and removing all of the cancer, and has been treated with chemo only, leaving those patients with a decreased prognosis and little hope for survival. The study prompts reconsideration of surgical treatment options in these patients and warrants further study into patient selection in this area, according to the lead researcher, Perry Shen. Researchers compared the outcomes of surgical removal of liver mets from crc, which is accepted as the treatment of choice, to the surgical removal of PSD from crc. The PSD removal was combined with intra-abdominal heated chemotherapy. They found that patients, who were able to undergo complete removal of all PSD, combined with heated chemo inside the abdomen, had no significant difference in survival rates than liver mets patients who underwent surgical removal. **This meant that surgical removal is a viable possibility for some patients with PSD where it had not been considered a good option before and can produce long term survival in select patients and should be considered as part of a multidisciplinary approach.**

Shen, Perry, et al., Peritoneal Surface Disease from Colorectal Cancer: Comparison with Hepatic Metastases Surgical Paradigm in Optimally Resected Patients. J of Surgical Oncology: Online Edition: 1534-4681. 2008

RADIATION

10. New Studies Improve Evidence Base For Colorectal Cancer Screening (Sept. 21/08)

The evidence supporting 2 colorectal cancer screening practices – the use of computed tomographic (CT) colonography as a screening tool and the use of a 5 year or longer rescreening period after a normal colonoscopy examination – has been strengthened by 2 new, large studies. The 2 studies appear in the September 18 issue of the New England Journal of Medicine. “These new data show that previous smaller studies’ results were not misleading with regard to the use and effectiveness of CT colonography as a screening method and of rescreening at five years or longer after a normal colonoscopy,” said Robert Fletcher, MD, professor emeritus at the Department of Ambulatory Care and Preventative Medicine, Harvard Medical School in Boston, Massachusetts, in an interview with Medscape Oncology. “Screening for colorectal cancer has lagged behind other screening, but it is now in a dynamic phase,” Dr. Fletcher wrote in an editorial accompanying the studies.

www.medscape.com/viewarticle/580713

11. Whole Brain Radiation of Brain Mets Leads to Memory Problems (Sept 30/08)

CRC patients whose cancer has spread to the brain experience more learning and memory problems when radiation to their whole brain follows more targeted radiotherapy. A study presented at the 2008 American Society for Radiation Therapy and Oncology annual meeting in Boston found that whole brain radiation after radiosurgery doubled the risk of cognitive problems. Stereotactic radiosurgery focused high amounts of radiation directly at brain tumours that had spread from primary cancer, including colorectal cancer. Whole brain radiation targeted wider areas in an attempt to destroy small, invisible metastases throughout the brain. Stereotactic radiosurgery is normally done in one high dose treatment while whole brain radiation therapy delivers lower doses over several weeks. Patients in the study received either stereotactic radiosurgery alone or stereotactic radiosurgery followed by whole brain radiation. However, the study was stopped after initial results showed that patients who were getting whole brain radiation had a 49% decline in learning and memory four months after their treatment began. Patients who only received stereotactic radiosurgery had a 23% decline. The lead researcher claims that stereotactic radiosurgery alone could become the standard of care for patients newly diagnosed with brain mets to best preserve their neurocognitive function.

More info about stereotactic radiosurgery from [RT Answers](#), a website for patients and families developed by ASTRO, the American Society for Therapeutic Radiology and Oncology.

Change, Eric, Phase III Randomized Clinical Trial of Radiosurgery with or without Whole brain Irradiation in Patients Newly Diagnosed with 1 to 3 Brain Metastases, ASTRO abstract, presented September 22, 2008.

OTHER

12. Rectal Cancer: What Induces Local Recurrence (Sept 22/08)

A research paper published in the World Journal of Gastroenterology explores the risk factors of local rectal cancer recurrence after curative resection in patients with middle to lower rectal carcinoma. The research team led by Dr. Wu Zy and his colleagues in the department of General Surgery, Guangdong Provincial People’s Hospital reported that local recurrence occurred in 12.5% of patients with middle and lower rectal cancer. Local recurrence was significantly associated with the following:

- a. Family history
- b. High CEA level
- c. Cancerous Perforation
- d. Tumour Differentiation
- e. Vessel Cancerous Emboli
- f. Circumferential Resection Margin Status

Zy, Wu, et al., Risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. World J Gastroenterology 2008; 14(30): 4805-4809

13. Significance of CEA and CA242 in the Diagnosis of CRC (Sept.22/08)

Carcinoembryonic antigen (CEA) is frequently used in the diagnosis of the colorectal carcinoma. CA242 is a novel unique tumour-associated antigen characterized by higher tumour specificity and sensitivity for crc, as compared with other mucin antigens. In a study published in the Chinese Journal of Cancer Research, preoperative levels of serum CEA and CA242 were

measured in 63 cases of crc. It was disclosed that the positive rate of CA242 was higher than that of CEA, particularly in patients with colon cancer. The combined determination of CEA and CA242 significantly increased the sensitivity and accuracy in the detection of colorectal cancer as compared with the use of CEA alone. In patients with advanced disease the positive rate was markedly elevated, especially in patients with liver mets. The results indicate that the combined use of CEA and CA242 assays is a useful adjunct diagnostic measure for colorectal carcinoma, and is helpful in the assessment of the stage of the disease as well as in making treatment plans.

Yu, Z, et al., Significance of CEA and CA242 in the diagnosis of crc. Chinese J of Cancer Research. Online Edition: 1993-0631. pp 272-275.

14. Lynch Syndrome Colon Cancers Show Better Survival (Sept 22/08)

A new study finds colorectal cancer patients with Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC) have better survival than patients without the inherited form of the disease. Overall, 94% of Lynch syndrome patients were alive five years after their diagnosis compared to 75% of those with sporadic cancer. Italian researchers studied all patients with crc treated at a cancer institute in Rome between 1970 and 1993. During that time, 40 patients, 25 women and 15 men, had Lynch syndrome. 573 patients, 312 women and 261 men had sporadic colon or rectal cancer. The lead researcher concluded that their results showed that overall survival of crc in patients with HNPCC is better than sporadic crc patients. The different outcome probably relates to the specific tumorigenesis involving DNA mismatch repair dysfunction. Lynch syndrome is an inherited cancer syndrome, passed directly from parent to child, and caused by mutations in the genes that repair damaged DNA. It is responsible for 3-5 % of crc, as well as some uterine, ovarian, and other associated cancers. Lynch syndrome colon cancers are usually diagnosed in younger people, in the right side of the colon, and have high microsatellite instability. Genetic testing can identify the genes that cause them to make a definite diagnosis.

Stigliano, Vittoria, et al., Survival of Hereditary Non Polyposis Colorectal Cancer Patients Compared with Sporadic Colorectal Cancer Patients. J of Experimental and Clinical Cancer Research, September 19, 2008. 27: 39

15. Exposing Cancer-Causing Gut Bacteria (Sept 23/08)

Scientists from the US have discovered that a molecule produced by a common gut bacterium (*Enterococcus faecalis*) activates signaling pathways that are associated with cancer cells. The research, published in the October issue of the *Journal of Medical Microbiology*, sheds light on the way gut bacteria can cause colon cancer. For several decades scientists have thought that some microbes living in the gut may play a role in the formation of sporadic colorectal cancer. *Enterococcus faecalis* is a normal gut bacterium. Unlike most gut bacteria, it can survive using two different types of metabolism: respiration and fermentation. When the bacteria use fermentation they release by-products. One of these is a kind of oxygen molecule called **superoxide (free radical)**, which can damage DNA and may play a role in the formation of colon tumours. The team found that 42 genes in epithelial cells in the gut are involved in the regulation of the cell cycle, cell death and signaling based on the unique metabolism of *E. faecalis*. This suggests that cells of the lining of the colon are rapidly affected when *E. faecalis* switches to fermentation. It also indicates that *E. faecalis* may have developed novel mechanisms to encourage colon cells to turn cancerous. The findings are the first to explore mechanisms by which normal gut bacteria damage DNA and alter gene regulation in the colon that might lead to cancer. The research puts in to perspective the complexity of the effects normal gut bacteria can have on the health of an individual.

www.medicalnewstoday.com/articles/122626.php

16. Digital Rectal Exam Poor Predictor of Rectal Cancer (Sept 29/08)

According to a recently published study from the UK, digital rectal exams are a poor way to accurately identify rectal cancer. When physicians examine the rectum with a gloved finger, they are unlikely to find a real tumour and more likely to refer patients unnecessarily for further tests. Doctors reviewed all referrals made to the urgent colorectal cancer system at University Hospital of North Staffordshire because of a palpable rectal tumour between May and December of 2006. Of 1,069 referrals to the system, 108 were for rectal tumours that general practitioners reported they felt during a digital rectal examination. However, after further testing, only 32 of those 108 exams actually was a rectal tumour. And 10 tumours, potentially within reach of the exam, were missed by referring general practitioners. Considering those referrals that actually were not tumours and the missed tumours, accuracy for digital rectal exam in finding very low

rectal cancer was 29%. Lead investigator concluded: Digital rectal examination is an inaccurate procedure and a poor predictor for palpable rectal tumour.

Ang et al., The diagnostic Value of Digital Rectal Examination in Primary Care for Palpable Rectal Tumour. Colorectal Disease, Volume 10, Number 8, October 2008, pp 789-792.

17. Physical Activity Influences Quality of Life in Colorectal Cancer Survivors (Oct 1/08)

A team of researchers examine the relationships of physical activity with quality of life among colorectal cancer survivors, reported in the latest J of Clinical Oncology. Physical activity can enhance quality of life for cancer survivors. Dr. Brigid Lynch and colleagues from Australia examined whether physical activity has a sustained effect on improvements in quality of life over 2 years after a colorectal cancer diagnosis. The team collected data within the Colorectal Cancer and Quality of Life Study, in which 1966 people diagnosed with crc were recruited through Queensland Cancer Registry. Participants completed telephone interviews at approximately 6, 12, and 24 months after diagnosis. The researchers found an overall independent association between physical activity and quality of life. At a given time point, participants achieving at least 150 minutes of physical activity per week had an 18% higher quality of life score than those who reported no physical activity. Dr. Lynch's team concluded: These findings suggest that the positive association between physical activity and quality of life is consistent over time. Encouraging crc survivors to be physically active may be a helpful strategy for enhancing quality of life.

Lynch, B et al., Physical Activity Influences Quality of Life in Colorectal cancer Patients. J Clinical Oncology. 2008; 26(27): 4480 – 4487.

NUTRITION

18. Effect of Omega-3 and -6 on Colorectal Adenoma Risk (Sept. 24/08)

Researchers from Wageningen University in the Netherlands have studied the relationship between omega 3 and 6 fatty acids and the risk for colorectal adenoma. 861 patients with colorectal adenoma or free of this condition were studied. Associations between omega 3 and omega 6 fatty acid blood levels and colorectal adenoma risk were made using endoscopy. Higher omega 3 blood levels were associated with a significantly lower risk of colorectal adenoma. Higher blood levels EPA and DHA (both omega-3's) and the omega 3/6 ratio were associated with lower colorectal adenoma risk, but not significantly. When the amount of omega 3 increases relative to omega 6, the ratio goes up. In contrast, increased total omega 6 fatty acids and linoleic acid (an unsaturated omega 6 fatty acid) were associated with a significant increase in the risk for colorectal adenoma.

Pot, Gerda, et al., Opposing Associations of Serum n-3 and n-6 polyunsaturated fatty acids with colorectal adenoma risk: An endoscopy based case-control study. International J of Cancer. Vol 123, Issue 8 pp 1974-1977.

19. Folic Acid Intake Affects Colon Cancer Risk (Oct 1/08)

Research from Scotland and the US has revealed a new explanation for the link between low folic acid intake and an increased risk of colon cancer. A depletion of folate causes increased DNA damage and prevents DNA repair. A lack of folate also influenced functional biomarkers of genomic stability such as cellular proliferation and apoptosis. The research reinforced the importance of folate, one of the B vitamins commonly called folic acid, and the argument for flour to be fortified with it as a matter of course. Ireland currently has one of the highest colorectal mortality rates in the developed world. The highest incidence of colorectal cancer is found in the southeast and northwest according to the National cancer Registry of Ireland (NCRI). The study found that adults with low folic acid intake have an increased chance of developing colon cancer. Former research showed that a deficiency of folate increased the risk of birth defects and this study showed that a reduced intake of folic acid causes DNA strands to break more frequently.

www.irishmedicalnews.ie/index.php/component/content/article/1-news

20. Vitamin C May Blunt Effect of Chemotherapy (Oct 1/08)

Dr. Mark Heaney of Memorial Sloan Kettering Cancer Center in New York and colleagues implanted human cancer cells into mice and found that when mice received vitamin C supplements two hours before chemo, the tumours grew more quickly. They tested 5 common chemo drugs: imatinib, doxorubicin, cisplatin, methotrexate and vincristine for leukemia and lymphoma. According to Dr. Heaney, the vitamin C didn't neutralize the effects of the chemo drugs, but it blunted their effects. Heaney said it did not appear that the antioxidant properties of

vitamin C were the culprit. Rather, it may be the protective effect vitamin C has on mitochondria (which generate energy for a cell) within cancer cells. Chemotherapy drugs damage mitochondria in cancer cells. When mitochondria are damaged, they can send signals to the cell to die. And that's one of the ways that the chemotherapy drugs exert their beneficial effects. And vitamin C helps to preserve the health of the mitochondria. Heaney acknowledged that a study looking at cancer cells in laboratory dishes or in mice is not the final word on the subject and said more research is required. (A study at the US National Institutes of Health published in August showed that injections of high doses of vitamin C greatly reduced the rate of tumour growth in mice.)

Heaney, Mark, et al., Vitamin C antagonizes the Cytotoxic Effects of Antineoplastic Drugs. Cancer Research. 68, 8031-8038, Oct. 1, 2008.