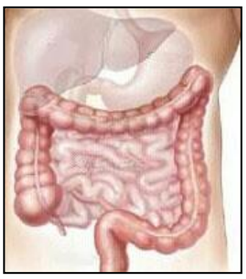
COLORECTAL CANCER RESEARCH UPDATES

Month Ending October 17th, 2012



The following colorectal cancer research update extends from September 15th, 2012 – October 17th, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. FDA Approves Regorafenib (Stivarga) for Metastatic Colorectal Cancer (Oct. 10/12)

Regorafenib (stivarga), an oral multikinase inhibitor, has been approved by the FDA to treat metastatic colorectal cancer. Regorafenib (stivarga) is a biologic drug in pill form which has a broader target than other biologics used to treat metastatic colorectal cancer patients. The approved indication is for the treatment of patients with metastatic colorectal cancer, "who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy (such as avastin), and, if KRAS wild type, an anti-EGFR therapy." Regorafenib is a drug in pill form that targets the VEGFR—a protein that stimulates growth of new blood vessels to nourish a tumor–and also RAF, a protein in the MAPK pathway that stimulates cell growth. Approval was based on the results of one study of 760 patients with metastatic colorectal cancer, who had been treated previously. Among those randomized to treatment with regorafenib and best supportive care, median overall survival was 6.4 months, compared with a median of 5 months among those who received placebo and best supportive care. Median progression-free survival was 2 months among those on regorafenib, compared with 1.7 months among those on placebo, according to the FDA statement announcing the approval. In June, CORRECT trial investigator Dr. Eric Van Cutsem of University Hospital Leuven in Gasthuisberg, Belgium, reported that regorafenib improved survival in *patients with KRAS mutations as well as those with wild-type KRAS*. "Regorafenib increases overall survival and progression-free survival in patients with metastatic colorectal cancer who have failed current standard therapies. The benefit is shown across pre-specified subgroups," he said at the American Society of Clinical Oncology annual meeting. Since patients whose tumors harbor Kras mutations have fewer treatment options due to resistance to the EGFR inhibitors cetuximab and panitumumab, this new agent should have particular utility for their treatment. Bayer HealthCare Pharmaceuticals will market the drug as **Stivarga**. The recommended dose is 160 mg, once daily for the first 21 days of each 28-day cycle. Regorafenib "is the latest colorectal cancer treatment to demonstrate an ability to extend patients' lives and is the second drug approved for patients with colorectal cancer in the past 2 months," Dr. Richard Pazdur, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research, said in the statement. In August, the FDA approved ziv-aflibercept (Zaltrap) for use in combination with a FOLFIRI (folinic acid, fluorouracil, and irinotecan) chemotherapy regimen for metastatic colorectal cancer. The most common adverse effects associated with regorafenib treatment included weakness or fatigue, loss of appetite, palmar-plantar erythrodysesthesia (hand and foot syndrome), diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia (hoarse voice), the FDA said. Regorafenib was approved within 6 months of the company's application for approval, under the FDA's review program for drugs that provide a major advance in treatment or provide a treatment for a disease for which there is no adequate treatment.

http://www.oncologystat.com/news/FDA_Approves_Regorafenib_for_Metastatic_Colorectal_Cancer__US.html

2. Addition of Aflibercept to 5FU + Leucovorin + Irinotecan (FOLFIRI) Improves Survival in a Phase III Study in Patients with Metastatic Colorectal Cancer (Sept. 19/12)

More than 8 years ago, bevacizumab (avastin) became the first anti-VEGF (vascular endothelial growth factor) agent when it was approved in conjunction with intravenous 5-FU–based chemotherapy as first-line treatment in patients with metastatic colorectal cancer (CRC). Now, in 2012, aflibercept (xaltrap) is entering the stage as an FDA-approved drug for use in patients with metastatic CRC who have failed first-line oxaliplatin-based chemotherapy. Aflibercept is a “designer-drug,” which is comprised of extracellular membrane components of VEGF-R1 and -R2, and thus binds VEGF-A (like bevacizumab), but also VEGF-B and PlGF (placental growth factor). The clinical data generated with aflibercept in CRC clearly demonstrate a survival benefit when this agent is used in second line in combination with FOLFIRI vs. FOLFIRI alone. The key question most relevant in clinical practice is if this effect could be superior to what can be achieved by using bevacizumab beyond progression, meaning continuing it from first- to second-line therapy, a strategy that was recently validated by prospective phase III data presented at ASCO 2012. Metastatic colorectal cancer is generally treated initially with a regimen of fluorouracil and leucovorin plus either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Patients cross over to the alternate regimen for second-line therapy. The antiangiogenic agent bevacizumab has been shown to increase survival in patients with metastatic colorectal cancer in the first-line setting when added to FOLFIRI and in the second-line setting when added to FOLFOX, but no biologic agent has been shown to improve survival in the second-line setting when added to FOLFIRI.

Van Cutsem, Eric, et al., Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Onc. Published online before print September 4, 2012.

3. Patient Preference Doesn’t Affect Chemo in Advanced CRC (Sept.19/12)

For patients with metastatic colorectal cancer (mCRC), most patients are treated with chemotherapy, even if they express negative or marginal preferences, according to the results of this study. Researchers conducted a prospective cohort study involving 702 patients with mCRC to determine how patient preferences guide the course of palliative chemotherapy. Overall, 91% of patients were treated by

a medical oncologist, and 82% of these received chemotherapy. The researchers found that patients aged 65 to 75 years or 75 years and older were less likely to visit an oncologist, as were those who were too unwell to complete their own survey. Patients who were 75 years or older with moderate or severe comorbidities or patients who were too unwell to complete their own survey were less likely to receive chemotherapy. Patients tended to receive chemotherapy even when they felt that treatment would not extend their lives (90%) or help them with their cancer-related problems (89%), and even when they stated a preference to focus on comfort rather than extending their life (90%). Treatment decisions in the palliative setting were not always congruent with stated preferences and beliefs regarding chemotherapy. The vast majority of patients who expressed negative or marginal preferences or beliefs regarding chemotherapy still received chemotherapy. Patient preferences and beliefs were not associated with the intensity or number of chemotherapy regimens received.

Zafar, Yousuf, et al., Chemotherapy use and patient treatment preferences in advanced colorectal cancer. Cancer. First published online September 12, 2012.

4. Should Aspirin Be Used to Help Prevent Colorectal Cancer? (Oct.3/12)

Aspirin, the everyday drug taken by countless people around the world to ward off pain and reduce their risk of developing heart disease, may serve another function -- preventing cancer. A growing body of evidence suggests that taking aspirin may reduce an individual's chances of developing colorectal cancer and perhaps other malignancies, but whether that evidence is strong enough to outweigh the risks of prescribing it to millions of healthy people is the subject of debate. At the ESMO 2012 Congress in Vienna, both sides of that debate are being aired in front of an audience of experts in one of the meeting's popular Controversy sessions. Arguing in favor of the question -- "Is aspirin (NSAID) ready for chemoprevention of colorectal adenoma/cancer?" -- is Prof Robert Benamouzig from the Department of Gastroenterology, Avicenne Hospital, Bobigny, France. "The efficacy of aspirin in preventing colorectal cancer has been made obvious by more than twenty years of research," said Prof Benamouzig. "In 2010, researchers published the 20-year follow-up of five pooled randomized trials that assessed the effect of aspirin on colorectal cancer incidence and mortality. The study of more than 14,000 patients found that daily aspirin at any dose reduced risk of colorectal cancer by 24% and associated deaths by 35% after a delay of about 8 to 10 years." "In these trials, the reduction of colorectal cancer rates was in essence a side-effect of treatment. None of them had such a reduction as their primary outcome. Nevertheless, the evidence that aspirin is effective for preventing these colorectal cancers is very strong," Prof Benamouzig said. Arguing that the answer to the question should be "No" is Prof Nadir Arber, Director of the Integrated Cancer Prevention at the Tel Aviv Sourasky Medical Center in Israel. "NSAIDs and in particular aspirin are very promising in secondary prevention of colorectal neoplasia, however their role in primary prevention is still not proven," Prof Arber said. "This means that the majority of the population does not need, and is not going to benefit from aspirin use. Having said that, specific high-risk populations definitely can benefit from aspirin intake, including people with hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, existing colorectal cancer or adenoma. In the future, based on genomic profile, we would be able to identify people who are at high risk of developing colorectal cancers and who might benefit from aspirin therapy." During the discussion, Prof Arber will present preliminary data showing how the efficacy and toxicity of aspirin in preventing cancer can be predicted based on some single nucleotide polymorphisms. Before aspirin can be used for preventing these cancers, we need to develop means of identifying people who are going to benefit from the drug without developing side effects, Prof Arber said. Risks of taking aspirin include gastrointestinal bleeding and intracranial hemorrhage. "We need a study that will measure overall morbidity and mortality and not efficacy and toxicity in a single organ or disease such as cardio-vascular disease," he said.

http://www.sciencedaily.com/releases/2012/10/121001084348.htm

5. Japanese Study of Radiologic Hepatic Arterial Infusion of 5FU Plus Systemic Irinotecan for Unresectable Hepatic Mets from CRC (Sept.24/12)

Treatment of patients who have metastatic colorectal cancer (CRC) by using a combination of hepatic arterial infusion chemotherapy (HAIC) and systemic chemotherapy has resulted in promising clinical outcomes. Additionally, image-guided HAIC is reported to be less invasive and distribute drugs more accurately than surgical HAIC. The purpose of this study was to assess the combination of image-guided delivery of fluorouracil through HAIC and systemic irinotecan in a multicenter phase I/II study. Twenty-five patients with unresectable liver metastases from CRC were fitted with hepatic arterial catheter and port systems by using image-guided methods. Intra-arterial 5FU (1,000 mg/m(2)) was administered on days 1, 8, and 15 of each treatment cycle. Systemic irinotecan was administered on days 1 and 15. No dose-limiting toxicity was encountered during phase I, and the recommended dose of irinotecan was set at 150 mg/m(2). The response rate and median survival time were 72% and 49.8 months respectively. Researchers concluded that the combination of image-guided delivery of 5FU (fluorouracil) through HAIC and systemic irinotecan yielded favorable safety, response rate, and survival results. They recommend that this combination should be evaluated in a large study.

Arai, Y, et al., Phase I/II study of radiologic hepatic arterial infusion of fluorouracil plus systemic irinotecan for unresectable hepatic metastases from colorectal cancer: japan clinical oncology group trial 0208-D1. J Vasc Intervent Radiol. 2012 Oct. 23; (10): pp. 1261-7

6. New Agent for Metastatic Colorectal Cancer (Oct. 10/12)

Maintenance therapy with a new immunomodulator agent called ***MGN1703*** improves progression-free survival over placebo in patients with metastatic colorectal cancer, according to a new study presented at the European Society for Medical Oncology (ESMO) congress in Vienna. An immunomodulatory or immunotherapy is a substance that has an effect on the immune system. Researchers presented results of an interim analysis of the phase II/III **IMPACT trial**. The analysis included 55 patients with metastatic colorectal cancer; all patients showed disease control—complete response, partial response, or stable disease—after 4.5 to 6 months of standard induction chemotherapy with FOLFOX/XELOX or FOLFIRI with or without bevacizumab (Avastin) regimens. The median progression-free survival was 5.8 months for patients receiving MGN1703 and 2.7 months for those who received placebo in a predefined target population (46 patients). Progression-free survival rates after 3 months of treatment also significantly favored MGN1703, at 43% vs. 8% for placebo. The 6- and 9-month rates of progression-free survival were also better in the MGN1703 group, at 34% vs. 8% and 22% vs. 0%, respectively. The apparent success of the maintenance therapy led to a discontinuation of randomization in the study. "These surprisingly positive results are equally highly innovative and clinically relevant in two ways: on the one hand, it is with MGN1703, a DNA immunomodulator, that the first representative of a whole new class of substances in colorectal cancer has been tested as efficacious in a randomized study," Dr. Arnold said. "And on the other hand, this is the second study ever which has tested the value of a proprietary maintenance therapy after another induction therapy." Drug-related adverse events included fever in three patients, as well as atypical pneumonia, muscle aching, arthralgia (joint pain), fatigue, paresthesia (skin burning), rash, and others. Researchers are planning a further clinical study to confirm the efficacy of MGN1703 in patients with metastatic colorectal cancer. The drug is an agonist of toll-like receptor 9 (TLR9), selectively attacking tumor cells and tumor-associated antigens following chemotherapy and radiation therapy. The company says its universal mechanism of action makes it a strong candidate against a number of different types of cancers.

http://www.cancernetwork.com/colorectal-cancer/content/article/10165/2107224

7. Memorial Sloan Kettering Will Not Offer Xaltrap to Their Patients (Oct.14/12)

Memorial Sloan-Kettering Cancer Center in New York made a very public announcement—and explanation — in a *New York Times* op-ed about why they will not offer the new drug Zaltrap® (ziv-aflibercept) to its metastatic colorectal cancer patients. The authors, all world-renowned cancer specialists at the world's oldest cancer center, in an op-ed headlined "In Cancer Care, Cost Matters," essentially challenged other cancer centers to take action where politicians fear to tread. 'We recently made a decision that should have been a no-brainer," wrote Drs. Peter B. Bach, Leonard B. Saltz and Robert E. Wittes. "The drug, Zaltrap, has proved to be no better than a similar medicine we already have for advanced colorectal cancer, while its price—at $11,063 on average for a month of treatment—is more than twice as high." The FDA approved Zaltrap in August for use in metastatic colorectal cancer (mCRC). Both Zaltrap (marketed by Sanofi and Regeneron) and Avastin® (bevacizumab, marketed by Genentech) work through a similar molecular mechanism, and when either medicine is added to standard chemotherapy, "either medicine has been shown to prolong patient lives by a median of 1.4 months." "In most other industries, something that offers no advantage…yet sells for twice the price would never even get on the market," they wrote. But health care is not like other industries. Medicare, as well as private insurers in most states, are required to cover a new drug once it receives FDA approval. But the FDA can only consider whether a new drug is "safe and effective"—not *more* effective, and costs cannot be considered by either the FDA or Medicare. The Memorial Sloan-Kettering Cancer Center leaders noted that their seemingly rational decision to use the less expensive, equally effective drug would likely be called "rationing, not rational" in a culture where no politicians seem willing to address rising costs of cancer. "But if no one else will act, leading cancer centers and other research hospitals should," they challenged their peers. "The future of our health care system, and of cancer care, depends on our using our limited resources wisely."

http://fightcolorectalcancer.org/research_news/2012/10/memorial_sloan-kettering_will_not_offer_zaltrap

SURGICAL THERAPIES

8. Participants Needed for Rectal Cancer Surgery Trial (Sept.28/12)

Approximately 80 more participants are needed for a multisite, Phase 3 clinical trial comparing laparoscopic-assisted versus conventional surgery in patients with stage IIA, stage IIIA or stage IIIB rectal cancer. Eligible participants must have completed their pre-surgery chemotherapy (Xelox™ or fluorouracil-based) and/or pre-surgery radiation therapy within the previous 4 weeks. Standard medical practice for rectal cancer surgery has been conventional operating techniques, but surgeons at comprehensive cancer centers around the world have been performing and studying outcomes of laparoscopic versus traditional rectal cancer surgery for several years. The evidence so far in most trials shows safety and recurrence rates about equal for both types of surgery; however, it's still too early to compare long-term survival rates. In this U.S. study, participants will be randomly assigned to receive either conventional surgery or laparoscopic-assisted surgery. During hospitalization for the surgery,

patients will be studied for surgical results (e.g., complete surgical removal of the cancer), as well as length of hospital stay and need for pain medication. For a follow-up period of several years, patients will fill out quality-of-life questionnaires (e.g., bowel, stoma, sexual function). The trial goal is to evaluate whether laparoscopic surgery is as safe and effective as conventional surgery to remove certain stage II and III rectal cancers. Outcomes will be evaluated according to surgical success, quality of life measures, and disease-free survival and/or pelvic recurrence within 2 years, with long-term follow-up for 5 years.

http://fightcolorectalcancer.org/research_news/2012/09/participants_needed_for_rectal_cancer_surgery_trial

9. World Ostomy Day – October 6, 2012 (Oct.6/12)

Saturday, October 6th was a day for people who live with ostomies to educate others and celebrate life with peers around the nation and world. Local ostomy support groups hosted open houses, picnics, educational meetings: The UOAA published a partial list of events and advocacy actions that took place around the nation.. At its annual Clinical Congress, the American College of Surgeons announced a new Ostomy Home Skills Kit for patients, including a sample to practice with, and for providers, a Skills Education Program providing evidence-based knowledge, checklists and skills training so patients can be prepared before surgery.

http://fightcolorectalcancer.org/research_news/2012/10/saturday_october_6_world_ostomy_day

10. Up-Front Hepatic Resection for Metastatic Colorectal Cancer (Oct.7/12)

Hepatic metastasis from colorectal cancer (CRC) is best managed with a multimodal approach; however, the optimal timing of liver resection in relation to administration of perioperative chemotherapy remains unclear. The researchers' strategy has been to offer up-front liver resection for patients with resectable hepatic metastases, followed by post-liver resection chemotherapy. They report the outcomes of patients based on this surgical approach. A retrospective review of all patients undergoing liver resection for CRC metastases over a 5-year period (2002-2007) was performed. A total of 320 patients underwent 336 liver resections. Median follow-up was 40 (range 8-80) months. The majority (n = 195, 60.9 %) had metachronous disease (metastatic disease showing up after the diagnosis of the colorectal primary tumour), and most patients (n = 286, 85 %) had a major liver resection (>3 segments). Thirty-six patients (11 %) received preoperative chemotherapy, predominantly for down-staging unresectable disease. Actual disease-free survival at 3 and 5 years was 46.2 % and 42 %, respectively. Actual overall survival (OS) at 3 and 5 years was 63.7 % and 55 %, respectively. Researchers concluded that up-front surgery for patients with resectable CRC liver metastases, followed by chemotherapy, can lead to favorable OS.

Cleary, S., et al., Up-front resection for metastatic colorectal cancer results in favorable long-term survival. Ann Surg Oncol 2012, Oct.5. Epub ahead of print.

RADIATION/INTERVENTIONAL RADIOLOGY

11. Laparoscopic Radiofrequency Ablation for the Management of Colorectal Liver Mets (Sept.19/12)

Published results addressing the treatment of colorectal liver metastases (CRLM) with radiofrequency ablation (RFA) vary widely with local recurrence rates of 2-40% and 5-year survival of 14-55%. The goal of this study was to analyze a 10-year experience with laparoscopic RFA. From January 2000 to July 2010, 130 patients underwent laparoscopic RFA for CRLM. In this cohort, median survival was 40.4 months with 5-year survival of 28.8%. Overall, 9.2% of patients had a local recurrence (3.6% for tumors 3 cm or less). Factors associated with decreased survival were

- BMI
- rectal primary and
- increased tumor size

The data demonstrate that laparoscopic RFA can achieve a median survival of 40.4 months with a low local recurrence rate. Patients with tumors 3 cm or less have a decreased risk of local recurrence.

Kennedy, TJ, et al., Laparoscopic radiofrequency ablation for the management of colorectal liver metastases: 10 year experience. J Surg Oncol 2012 Sep 20. Epub ahead of print.

12. Treating Lung Mets With Radiofrequency Ablation (Oct.16/12)

Radiofrequency ablation (RFA) has emerged as a potential, lung function-preserving treatment of colorectal lung metastases. Forty-five patients with colorectal pulmonary metastases underwent CT-guided RFA from December 2004 to June 2010. A baseline post treatment scan was obtained 4-6 weeks after RFA and follow-up imaging studies every 3 months thereafter were obtained and compared to evaluate the tumor progression at the site where RFA had been performed or elsewhere. The primary end points were Lung Tumour Progression-free survival and overall survival from RFA procedure. Sixty-nine metastases were ablated in 45 patients. Tumor size ranged from 0.4 to 3.5 cm. The median number of metastases ablated per patient was 1 (range, 1-3). Median follow-up after RFA was 18 months.

Median survival from the time of RFA was 46 months. One-, 2- and 3-year overall survival rates from the time of RFA were 95%, 72%, and 50% respectively. Nine of 69 lesions (13%) progressed and 4 were retreated with no progression after second RFA. Median time to progression was not reached. Lung Tumour Progression-free survival from RFA was 92% at 1 year, 77% at 2 years, and 77% at 3 years. The researchers concluded that radiofrequency ablation of lung metastases is an effective minimally invasive, tissue-sparing technique that has very good local control rates in patients with pulmonary metastases from colorectal cancer, with LTP-free survival of 77% at 3 years.

Petre, EN, et al., Treatment of pulmonary colorectal metastases by radiofrequency ablation. Clin Colorect Cancer. 2012 September 28; Epub Ahead of Print.

SCREENING

13. Cancer Detection Test Could Soon Be Available in Canada (Sept.24/12)

Canadian healthcare providers could soon have access to a powerful new laboratory test for the detection and ongoing management of four common types of cancer, including those from lung, prostate, breast and **colon.** This test could be used by physicians in the workup of a suspected cancer case; and may also be employed to monitor remission and recurrence. The simple blood test detects the presence of the **human aspartyl (asparaginyl) beta-hydroxylase (HAAH),** a novel biomarker expressed in malignant cancer cells, in patients' blood samples. HAAH levels are measured using an ELISA assay. In a double blind study of 857 samples, conducted previously by the biotech company Panacea, the test showed 94.7% sensitivity, 94.3% specificity and an overall accuracy of 94.6%. Recently three papers were presented by Panacea Global Inc. at the World Cancer Congress in Montreal, Canada, 2012; and at the 5th Oncology Biomarkers Conference, Zurich, Switzerland, 2012. These were entitled

- "**Early Diagnosis of Cancer; HAAH-Based Serum Immunoassay",**
- **"HAAH-based monitoring of Cancer Remission/Recurrence" and**
- **"HAAH: A Biomarker for Companion Diagnostics in Breast, Lung, Prostate, and Colorectal Cancer".**

Therefore, doctors who suspect the presence of cancer in a patient may soon have a simple, cost effective and quick test to aid in the diagnosis of cancer. Furthermore oncologists may soon be able to monitor the levels of HAAH, as an indicator of remission or recurrence of disease. **Panacea Global Inc** has signed an exclusive three year laboratory service agreement with Gamma-Dynacare Medical Laboratories to establish and perform the ELISA assays; and will perform additional clinical trials confirming the efficacy of the test. "Once the assay is fully established, we will be one step closer to making this unique test available to Canadians", commented Dr. Mahmood Moshiri, President and CEO of Panacea Global Inc. (PANG-OTCBB,).

http://www.panaceaglobalinc.com/breakthrough-cancer-detection-test-could-soon-be-available-in-canada/

14. New Colonoscopy Surveillance Guidelines Issued by U.S. GI Societies (Oct.4/12)

The U.S. Multi-Society Task Force on Colorectal Cancer has released a consensus update regarding colonoscopy surveillance—and the guidelines indicate that average-risk patients who have a clean colonoscopy can wait 10 years between exams. Colorectal cancer often begins with the development of an adenomatous polyp. These polyps often take 10 to 15 years to transform into cancer. Because this development phase is so long, screening and early detection can play a role in the prevention of colorectal cancer, as detection and removal of the polyps can prevent the development of the disease. For people at average risk of colorectal cancer, the American Cancer Society recommends that routine screening begin at age 50. There are many screening tests available, but colonoscopy remains the gold standard. During a colonoscopy, a physician examines the full length of the large intestine and removes polyps. The recommended interval between colonoscopies—sometimes referred to as surveillance—varies depending on the individual results of the test. In general, a higher rate of polyps leads to a recommendation for shorter screening intervals. Guidelines for colorectal cancer surveillance were published in 2006. The U.S. Multisociety Task Force—which is comprised of representatives of the American College of Gastroenterology, the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy—recently evaluated those guidelines to determine if they should change based on new data. What they found was that new evidence supported the existing guidelines. Although the guidelines will continue to be evaluated as new evidence becomes available, for now the task force recommends the following surveillance schedule:

If the initial exam finds:	Then, the next colonoscopy should take place in:
No polyps or small (<10 mm) hyperplastic polyps in the rectum or sigmoid colon	10 years
Low-risk adenomas defined as 1-2 tubular	5-10 years

adenomas <10mm	
Serrated lesion <10mm, non-dysplastic	5 years
Benign, but high-risk neoplastic polyps, including: adenoma >10mm, or with villous histology, high grade dysplasia; three or more adenomas; sessile serrated lesions which are dysplastic and/or >10mm	3 years

The full guidelines are quite detailed and provide thorough advice on all aspects of colorectal cancer screening. Some other highlights include:

- If the patient's bowel is not properly prepared for colonoscopy, repeat the exam within one year.
- Surveillance colonoscopy need not be modified based on race, ethnicity, or sex—despite data indicating that African-Americans are at higher risk for colorectal cancer.
- Surveillance intervals should not be changed due to use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). These drugs have been shown to reduce the risk of polyps—but there is no evidence to indicate that their use should result in shorter screening intervals.
- Surveillance colonoscopy in the elderly should be determined on an individualized basis.

Lieberman DA, et al. Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer.* Gastroenterology *2012; September; 143(3): 844-857.

OTHER

15. Marriage Impacts the Use of Colorectal Endoscopy Exam (Oct.1/12)

This study examined the association between marriage and colorectal endoscopy exam (colonoscopy), and whether this association varies by gender and financial benefits of marriage including improved access to health insurance and pooled family income. Data were used from the 2000, 2005, and 2008 U.S. National Health Interview Survey. Analyses targeted 21,760 persons 50–85 years of age without a personal history of cancer and with complete information on all study variables. According to the results, married persons were more likely than unmarried persons to report ever having undergone a colorectal endoscopy exam, and the difference between married and unmarried persons in the probability of undergoing a colorectal endoscopy exam remained stable over time. Married persons were more likely than unmarried persons to report having undergone a colorectal endoscopy exam within the past 10 years. For each survey year, married men were significantly more likely than women and unmarried men to report having undergone a colorectal endoscopy exam. For example, in 2008, 56% of married men reported having undergone a colorectal endoscopy exam, compared to 49% of unmarried men, 52% of married women, and 50% of unmarried women. Among persons with health insurance, married persons were significantly more likely than unmarried persons to have undergone a colorectal endoscopy exam. Among persons who were poor, there was no difference by marital status in the likelihood of having undergone a colorectal endoscopy exam. However, among persons who were not poor, married persons were more likely than unmarried persons to have undergone a colorectal endoscopy exam. Given that colorectal endoscopy exams are a potentially life-saving procedure, persistently higher uptake of colorectal endoscopy for married persons over time may be an important health promoting benefit of marriage. Therefore, the researchers maintain that clinicians and policy makers should focus on improving the use of cancer prevention services among unmarried persons.

Stimpson, Jim, et al., The effect of marriage on utilization of colorectal endoscopy exam in the United States. Cancer Epidemiology. 2012 Oct 1; 36(5)

16. Patient Involvement in Decision-Making (Oct.10/12)

What happens when patients get to read their own medical records? The Oct. 2nd issue of *Annals of Internal Medicine* published two editorials and results of a quasi-experimental trial of 100 primary care doctors who voluntarily provided 13,500 patient volunteers with access to their doctors' notes for a year. These are some of the results in brief:

- patients loved being able to read their visit report, and 75% said they were more likely to take medicines as directed;
- doctors didn't see increased patient anxiety, visits, or time demands.

Meanwhile, an expert panel of "thought leaders" gathered by the Institute of Medicine released an in-depth report about helping patients make better care decisions by giving them the best available medical evidence. The results, summarized in an online *JAMA* article and discussed by Dr. Robert Miller for ASCO Connections, included:

- 8 in 10 patients want their provider to listen, but only 6 in 10 say it happens;

- 8 in 10 want to hear the full truth about their diagnosis;
- fewer than half of patients say their provider asks about their goals and concerns.

The Open Notes study, described in the Oct. 2 2012 Annals of Internal Medicine , is "quasi-experimental" because participants (both patients and primary care doctors) were volunteers who had access to electronic records, and it was done in only 3 geographic areas (Boston, Seattle and Pennsylvania). But it is one of the first carefully reported observations of open-access medical records. Before the study, doctors who volunteered and those who declined to participate said they worried about disrupted workflow and that the notes would confuse or worry patients, according to a previously published study . In striking contrast, about 99% of patients were eager to get access to their doctors' visit notes. After the year-long experiment, the vast majority of patients had read at least one note and about half of those completed a post-survey:

- 77-87% of patients said open notes helped them feel more in control of their care;
- 60-78% of those taking medicines reported they followed medication directions better;
- Only 1-8% reported confusion, worry or offense; and
- Surprisingly, 20-42% reported sharing notes with family or friends.

Among participating doctors, 0-8% reported longer clinic visits or more time spent answering patient questions via emails; and 0-14% reported spending more time writing notes. Interestingly, about 60% of patients believed they should be able to add comments to the doctors' notes, and 99% wanted open notes to continue and no participating doctor decided to stop providing access. "Traditionally, the patient's physician generates the first opinion, with other clinicians offering second opinions. However, an opinion at least as important must also be recognized in this traditional rubric–that of the patient and family," wrote the authors in summarizing results of an Institute of Medicine (IOM) expert report on how to better communicate medical evidence to both providers and patients. The report resulted from an IOM initiative to understand Americans' desire to develop their own informed opinions and be included in decision-making about their own care. They performed a nationally representative poll whose findings included:

- 9 in 10 patients want their clinician to offer choices for tests and treatments—and not just the option that their physician recommends;
- nearly half strongly wanted to discuss the option of doing nothing; and
- 97% want coordinated care, but only 54% felt they got it.

The complete report includes explanations preferred by focus groups, and more. A health care system "can deliver truly patient-centered care only when patient preferences—informed by medical evidence and provider expertise—are elicited, integrated, and honored," the authors wrote. In an ASCO commentary , Dr. Robert Miller, a "busy clinician in a breast cancer practice at an academic medical center," shared his honest reactions, including the admission that "…my colleagues and I probably aren't hitting the mark nearly as often as we would like to give ourselves credit."

http://fightcolorectalcancer.org/policy_news/2012/10/patient_involvement_in_decision-making_a_long_way_to_go#more-17151

17. Elevated CEA Levels and Low Distance of Tumour from The Anal Verge May Be Predictors of Lack of Response to Chemoradiation (Oct.16/12)

The objective of this study was to evaluate predictive factors for complete response after long-term chemoradiotherapy (RCT) for rectal cancer. Tumor down staging after RCT for rectal cancer can be obtained in half of cases, whereas a complete response to treatment is reported to range between 15 and 30%. It is not possible to foresee before therapies who will respond to chemoradiation. Patients with stage II-III rectal cancer that had undergone RCT and rectal resection between January 1995 and October 2010 were studied. Patients were divided in those who achieved a complete response, "CR" group, and those who did not achieve a complete response, "NCR" group. Analyses between groups were performed considering the clinical parameters:

- gender,
- age,
- ASA score,
- preoperative hematic CEA,
- tumor grading,
- distance of the tumor from the anal verge,
- maximum tumor diameter,
- TNM stage, and
- neoadjuvant treatment details.

Among 260 patients, 43 (16.5 %) achieved a complete response to chemoradiation. A CEA <5 ng/dl and distance from anal verge >5 cm were correlated with complete response. Patients with **both** these conditions ***presented a significantly higher complete response rate (30.6 %) as well as improved 5-year survival***. A complete response was also correlated with improved survival. Researchers concluded that very low tumors with a high serum CEA are very unlikely to reach a complete response.

NUTRITION & HEALTHY LIFESTYLE

18. Updated Evidence For Colorectal Cancer: Diet & Cancer Report (Sept.24/12)

The research team at Imperial College London produced a report of the updated evidence on food, nutrition and physical activity in relation to the prevention of colorectal cancer in 2010. The review added 263 papers and updated meta-analyses for whole grains, fruits and vegetables, meat and fish, dairy foods, alcohol, dietary fibre, glycemic index, folate, vitamin D, haem iron, calcium, physical activity, body mass index, abdominal fatness and adult attained height. The Panel considered the updated evidence and agreed that the updated CUP findings confirmed or strengthened the convincing and probable conclusions of the Second Expert Report for colorectal cancer. The Panel agreed that the evidence for a protective effect from foods containing dietary fibre had strengthened and could be upgraded to convincing. Conclusions for other factors previously judged to be convincing or probable were confirmed. A CUP 2011 Summary updates the colorectal cancer section of the Second Expert Report and is based on the findings of the 2010 report and the Expert Panel discussion. The Panel's judgments for factors graded convincing and probable are shown below. Further details on other factors can be found in the 2011 Summary. Information on how the Panel judged the evidence can be found in chapter 3 of the Second Expert Report.

Convincing and probable conclusions from the **Continuous Update Project report on colorectal cancer***

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE COLON AND THE RECTUM

	DECREASES RISK	INCREASES RISK
Convincing	Physical activity[1,2] Foods containing dietary fibre[3]	Red meat[4] Processed meat[5] Alcoholic drinks (men)[6] Body fatness Abdominal fatness Adult attained height[7]
Probable	Garlic Milk[8] Calcium[9]	Alcoholic drinks (women)[6]

1 Physical activity of all types: occupational, household, transport, and recreational.
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.
4 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 The judgements for men and women are different because there are fewer data for women. For colorectal and colon cancers the effect appears stronger in men than in women.
7 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
8 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.
9 The evidence is derived from studies using supplements at a dose of 1200 mg/day.

*WCRF/AICR Continuous Update Project 2011

http://www.dietandcancerreport.org/cup/current_progress/colorectal_cancer.php

19. Eating Veggies Could Slow Cancer (Sept.28/12)

New research has found that dozens of plant-based compounds can slow the spread of many common cancers – including breast, skin, lung, prostate, **colorectal** and others – by turning on cancer-fighting,

metastasis suppressor genes. The study author has identified more than 40 plant-based compounds that help slow the progression of cancer. They include:

- glucosinolates – found in cruciferous vegetables such as broccoli, cabbage, cauliflower and kale;
- lycopene – the bright-red carotenoid found in tomatoes, watermelon, papaya and pink grapefruit;
- lupulone – a flavonoid found in hops;
- curcumin – found in turmeric; and
- pomegranate juice.

The study author used existing cancer studies to survey information on metastasis-suppressor genes, which was often buried in reports focused on other areas of cancer research. He said most cancer studies concentrated either on preventing cancer or treating the initial tumour but little work had been done to understand how cancer spreads to other organs – that is, when it metastasized. "Very surprised that there had been little specific research in this area and very little to specifically look at the interaction between diet and lifestyle and their effects on these genes

Meadows, Gary. Diet, nutrients, phytochemicals, and cancer metastasis suppressor genes. Cancer and Metastasis Reviews. Dec. 2012, Vol. 31, Issue 3-4: pp.441-454

20. Cruciferous Vegetables Help To Prevent Colorectal Cancer (Oct.1/12)

The results of this study suggest that eating lots of cruciferous vegetables can significantly reduce risk of developing many types of cancer including oral cancer, esophageal cancer, **colorectal cancer**, breast cancer and kidney cancer. Cruciferous vegetables, from the vegetable family Brassicaceae, include:

- bok choy
- watercress
- broccoli
- sprouts
- cauliflower
- radish
- cabbage

Epidemiological studies have shown that eating cruciferous vegetables was associated with reduced risk for a number of cancers, but not all studies were consistent. Researchers conducted the current meta-analysis of data from multiple case-control studies conducted in Italy and Switzerland to examine the association between consumption of cruciferous vegetables and risk of multiple cancers. The meta-analysis included:

- 1468 cancers of the oral cavity/pharynx,
- 505 of the esophagus,
- 230 of the stomach,
- **2390 of the colorectum**,
- 185 of the liver,
- 326 of the pancreas,
- 852 of the larynx,
- 3034 of the breast,
- 367 of the endometrium,
- 1031 of the ovary,
- 1294 of the prostate,
- 767 of the kidney, and
- 11 492 controls

Both cancer patients and controls were accepted in the same network of hospitals for treatments and controls were admitted for a wide range of acute non-cancerous health conditions. Compared to men and women who ate no cruciferous vegetables, those who ate cruciferous vegetables at least once a week cut their risk of cancer of the

- oral cavity/pharynx by 17%,
- esophageal cancer by 28%,
- colorectal cancer by 17%,
- breast cancer by 17%, and
- kidney cancer by 32 %.

In addition, eating cruciferous vegetables, compared to eating no cruciferous vegetables, cut risk of

- stomach cancer by 10%,
- pancreatic cancer by 10%,
- laryngeal cancer by 16%,
- endometrial cancer by 7%,
- ovarian cancer by 9%, and
- prostate cancer by 13%.

But these risk reductions are not statistically significant. The researchers concluded: "This large series of studies provides additional evidence of a favorable effect of cruciferous vegetables on several common cancers."

Bosetti, C et al. Cruciferous vegetables and cancer risk in a network of case-control studies Ann Oncol (2012) 23(8): 2198-2203

21. Long Term Folate Supplementation Cuts Colorectal Cancer Risk (Oct.9/12)

Taking folate or folic acid supplements may reduce risk of colorectal cancer, according to the results of this study. Researchers found those who had used folate supplements for a long time were at 45% reduced risk for colorectal cancer. Previous studies have suggested folate may lower risk of colorectal cancer although studies are inconsistent with some pointing to the possibility that the naturally occurring dietary folate differs from the synthetic form of the vitamin called folic acid. Folic acid and folate are often used interchangeably because it is assumed that their nutritional values are the same although chemically they are two different chemicals. The current study is interesting. The researchers wanted to examine how dietary folate and supplemented folic acid would be associated with risk of cancers on the left and right sides of the colorectum. Research has already suggested that cancers on the left side and on the right side are different in terms of their phenotypes and they may have different sets of risk factors, according to the researchers. The population-based case-control study conducted in Western Australia involved 850 cases of colorectal cancer with 575 left-sided and 275 right-sided and 958 controls. A statistical analysis showed that natural dietary folate intake was not associated with risk of either left-or right-sided colorectal cancer and use of folic acid supplements similarly did not seem to have a significant effect on right-sided colorectal cancer. However, ***individuals who had used folate supplements for more than 4 years had a 45% reduced risk of left-sided colorectal cancer, compared to those who had not taken folic acid supplements.*** A significant trend in risk reduction was observed as duration of use increased. Folate is a vitamin found high in plant-based foods, particularly green vegetables. Many processed foods are fortified with folate and too much fortified folate may not be good for a person's health, according to previous studies.

Clapin, Helen, et al., Dietary and supplemental folate and the risk of left and right sided colorectal cancer. Nutrition and Cancer. Vol. 64, Issue 7, 2012. Pp. 937-945.

22. Magnesium May Reduce Colon Cancer Risk (Oct.9/12)

Individuals who consume a diet high in magnesium-rich foods, such as green leafy vegetables, beans and seeds, may reduce their risk of colorectal cancer by as much as 11% compared to those with low dietary magnesium intake, according to this new study. Researchers conducted a meta-analysis to determine whether higher dietary magnesium intake is associated with reduced colorectal cancer risk. They identified eight prospective studies of magnesium intake in relation to colorectal cancer risk. The studies contained information from 338,979 participants; data was available for 8,000 cases of colorectal cancer. They found individuals who had the highest average dietary intakes of magnesium had an 11% reduction in colorectal cancer risk, compared to those with the lowest average intakes. Restricting the analysis to six studies that have adjusted for calcium intake, results showed the risks of colon and rectal cancer were 19% and 6% lower, respectively, for the highest average magnesium intakes. Results indicated that for every 50 mg per day increase in intake of the mineral, the risk of colon cancer was reduced by 7%.

Chen, GC., et al., magnesium intake and risk of colorectal cnacer: a meta-analysis of prospective studies. European J of Clin Nutrition. Published online ahead of print.

23. Drinking Milk May Protect from Colon Cancer Progression (Oct.9/12)

A protein that exists in milk can significantly reduce the rate at which colon cancer cells grow over time. Researchers found that Lfcin4-14 (lactoferricin4-14), a milk protein which researchers have known has several health benefits, considerably reduces the growth rate of colon cancer cells over the long term. The protein extends the cell cycle period before chromosomes are replicated. The authors explained that treatment with lactoferricin4-14 reduced DNA damage in colon cancer cells caused by exposure to UV light. Lead study author wrote: *"We previously hypothesized that the prolongation of the cell cycle in colon cancer cells as a result of Lfcin4-14 treatment may give the cells extra time for DNA repair. Indeed, UV light-induced damage was decreased in colon cancer cells treated with Lfcin4-14 compared with controls. The differences were small but significant."* The scientists first exposed the colon cancer cells to UV light, which damaged their DNA. They then grew the cells either with Lfcin4-14 present or without it. DNA damage was assessed by using comet assay - a sensitive measuring technique. After being processed, the DNA-damaged cells look like a comet, with its characteristic tail. The ratio of the tail-intensity to the comet head indicates how extensive the DNA damage is. When exposed to UV light there were more comets. However, after being exposed to Lfcin4-14, the number of comets in the UV light-exposed cells went down. The researchers wanted to find out which mechanism Lfcin4-14 used to reduce DNA damage. They evaluated the levels of a number of proteins involved in cell cycle progression, DNA repair, and cell death. They found a rise in **flap endonuclease-1**, a protein linked to DNA synthesis; a drop in b-cell lymphoma 2-associated X protein, which plays an important role in cell death; and a fall in the level of **-H2AX**, suggesting improved DNA repair. Authors wrote: "These changes in expression support our hypothesis that Lfcin4-14 treatment resulted in increased DNA repair." Cancer cells typically have flaws in their DNA repair mechanisms. Study authors concluded: *"Our data*

suggest that the effects of Lfcin4-14 in prolonging the cell cycle may contribute to the cancer preventive effect of milk. This must be further investigated in different systems."

Oredssone, S., et al., Reduction of ultraviolet light-induced DNA damage in human colon cancer cells treated with lactoferrin-derived peptide. J of Dairy Science. Vol 95, Issue 10: pp. 5552-5560.

24. Alcohol Consumption and Colorectal Cancer (Oct.11/12)

People who drink alcohol increase their risk of erectile dysfunction, liver disease, breast cancer, pancreatic cancer and a few other cancers. **Colorectal cancer** joins the list with a new study showing a significant increase in the risk of colorectal cancer based upon how much alcohol a person drinks. This study found that the risk of colorectal cancer increases 21% for moderate drinkers (2–3 drinks/day) and 52% for heavy drinkers (≥4 drinks/day). The increased risk of colorectal cancer was higher for male moderate drinkers (24%) than for female moderate drinkers (8%). Persistent drinking takes a toll on the human body, in addition to the potential damage to a person's emotions and relationships.

Fedirko, V, et al., Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Annals of Oncology. 22(9): pp. 1958-1972.

25. B Vitamins and Folic Acid Do Not Reduce Colorectal Adenoma Risk (Oct.12/12)

Dietary supplements are extremely popular throughout the world, and especially in the USA. According to some studies, between 28% and 35% of Americans said they take dietary supplements which contain vitamins B_6, B_{12} and folic acid. Prior animal studies have demonstrated that B vitamins help fight colorectal carcinogenesis (initiation of cancer formation). Some epidemiologic studies had indicated that those consuming the most folate had a 20% to 40% lower-than-average risk of developing colorectal cancer. However, the vast majority of studies have concentrated on the benefits of just folic acid supplementation. Researchers set out to find out what the impact of taking vitamins B_6, B_{12} and folic acid supplements might be on colorectal adenoma risk. Colorectal adenomas are benign tumors. Although they may be benign, they can eventually become malignant over time. When they become malignant they are called adenocarcinomas. Even during their benign state they can still cause serious health problems by pushing against other structures. In this study, the team carried out a study in WAFACS (the Women's Antioxidant and Folic Acid Cardiovascular Study). This randomized, double-blind, placebo-controlled study involved 5,442 female health care professionals who were deemed to be at high risk of cardiovascular disease. The study lasted from April 1998 to July 2005. The women were randomly selected into one of two groups:

- The combination supplement group - they were given vitamins B_6, B_{12} and folic acid
- The placebo group

A follow-up endoscopy during the 9.2 year monitoring period was performed on 1,470 of the participants. Vitamins B_6, B_{12} and folic acid made no significant difference to adenoma risk. The authors found no statistically significant change in the risk of developing colorectal adenoma between the young women in the two groups, i.e. **the vitamin B_6, B_{12} and folic combo supplementation does not appear to reduce colorectal adenoma incidence**. The researchers wrote: *"Our findings do not support recommending B-vitamin supplementation for the prevention of colorectal adenomas."* They emphasized that further evidence is required to confirm the findings from this latest study. And added that alcohol consumption did not alter the impact the supplements had on their results. Alcohol is a known folate antagonist.

Song, Yiqing, et al., Effect of combined folic acid, vitamin B6, and vitamin B12 on colorectal adenoma. J of the National Cancer Institute. October 12, 2012. DOI: 10.1093/jnci/djs370