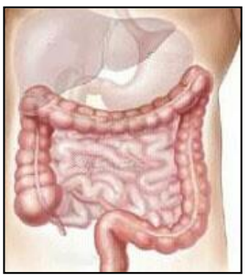
COLORECTAL CANCER RESEARCH UPDATES

Month Ending January 16th, 2015



The following colorectal cancer research update extends from October 18th, 2014 – January 16th, 2015 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. FDA Fast Tracks Combination Metastatic Colorectal Cancer Drug (Oct.20/14)

Taiho Oncology announced that the FDA has granted Fast Track designation for trifluridine and tipiracil hydrochloride (***TAS-102***), an oral combination anticancer drug for the treatment of refractory metastatic colorectal cancer (mCRC). Taiho Oncology has initiated a rolling New Drug Application (NDA) submission to the FDA for TAS-102. The NDA submission was based on a Phase 3 RECOURSE trial of TAS-102 in 800 patients affected with mCRC, whose disease had progressed after or who were intolerant to standard therapies.

About TAS-102
TAS-102 is an oral combination investigational anticancer drug of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

http://www.empr.com/fda-fast-tracks-combination-metastatic-colorectal-cancer-drug/article/378097/

2. Folfoxiri + Avastin Shows Improved Outcomes in Metastatic Colorectal Cancer (Oct. 23/14)

According to a recent report in *The New England Journal of Medicine*, initial treatment with FOLFOXIRI plus Avastin® (bevacizumab), rather than FOLFIRI plus Avastin, improved progression-free survival in adults with inoperable metastatic colorectal cancer. A standard initial therapy for advanced colorectal cancer is FOLFIRI (fluorouracil plus leucovorin and irinotecan) plus bevacizumab (256 patients). The investigators hoped to improve the outcomes obtained with FOLFIRI by adding an additional chemotherapy agent, oxaliplatin to the regimen. This experimental regimen, FOLFOXIRI (fluorouracil plus leucovorin and irinotecan and oxaliplatin) plus bevacizumab was directly compared to FOLFIRI in the clinical study. Overall 508 patients with unresectable metastatic colorectal cancer who had not received previous chemotherapy or biologic therapy for their metastatic disease were treated at 34 medical centers across Italy. Both groups received maintenance therapy with fluorouracil plus Avastin® until the cancer progressed or they withdrew from the study. Study participants had been followed for an average of 32 months at the time of publication. Individuals treated with FOLFOXIRI were more likely to develop some side effects including neutropenia, diarrhea, stomatitis, and peripheral neuropathy. FOLFOXIRI treated patients survived longer and experienced a delay in cancer progression compared to those treated with FOLFIRI. Median overall survival was 5 months longer with FOLFOXIRI and survival without cancer progression was 12.1 months with FOLFOXIRI compared to 9.7 months with FOLFIRI.

Loupakis, Fotios, et al., Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal CancerN. Engl. J. Med. 2014 Oct. 23 [doi:10.1056/NEJMoa1403108]

3. Using Oncolytic Viruses to Treat Metastatic Disease (Oct.31/14)

The following article is courtesy of Brad Thompson, PhD., Chairman, President and CEO of Oncolytics Biotech Inc. In Calgary, AB.

Could a virus be the key to finally beating metastatic disease? The question is not as odd as it might sound. Virotherapy or oncolytic virus therapy involves the conversion of viruses into cancer-fighting agents by reprogramming them to attack cancerous cells, while healthy cells remain relatively undamaged. Specifically, viruses can be harnessed to infect, multiply within and subsequently lyse cancer cells; the virus targets the tumor and protects normal tissue. Several types of oncolytic viruses have been developed to date. One of them, the reovirus, is a non-enveloped virus with a double-stranded, segmented RNA genome that forms particles that are 60 to 90 nm. The reovirus preferentially replicates in cancer cells that feature a common mutation known as an “activated Ras pathway,” while sparing normal cells. This makes it intrinsically tumor selective without the need for any genetic manipulation.

How Reoviruses Might Help

Reovirus is a virus with no known associated disease. It replicates in the cytoplasm and therefore does not integrate into the cell’s DNA. Reovirus is found everywhere in nature and has been isolated from untreated sewage, river and stagnant waters. Exposure to reovirus is common in humans, with half of all children by the age of 12 having been exposed and up to 100 percent testing positive by adulthood. Tumors bearing an activated Ras pathway can’t activate the antiviral response mediated by the host cellular protein, PKR. Studies have shown that reovirus actively replicates in transformed cell lines with an active Ras signaling pathway, eventually killing the host cell and freeing the viral progeny that go on to infect and kill more tumor cells. When normal cells are infected with reovirus, the immune system can neutralize the virus. Approximately one-third of human cancers have activating mutations in the Ras gene itself, and it is possible that more than two-thirds of cancer cells have an activated Ras signaling pathway because of activating mutations in genes upstream or downstream of Ras. Although it has been demonstrated in animal studies that reovirus is capable of treating metastatic cancer in immunocompetent mice, it has also been shown that reovirus used in conjunction with immunosuppressive drugs can effectively prolong animal survival. Combining intravenous reovirus therapy with Cyclosporine A, an immune suppressant, significantly inhibited tumor regrowth. In a model of

disseminated LLC metastatic lung cancer in C57BL mice, treatment with reovirus and either Cyclosporine A or T cell depleting antibodies (anti-CD4 and anti-CD8 Ab) led to an increase in survival compared to treatment with reovirus alone. The above results supported the development of clinical protocols in which immune suppressive drugs could be combined with a systemically administered reovirus in the treatment of cancer. Combining reovirus with various chemotherapies in human colorectal cancer cell lines demonstrated synergistic cytotoxic activity. In addition to modulating the immune response, the use of chemotherapies along with reovirus treatment may enhance intratumoral spread of the virus. Clinical trials of a proprietary variant of the reovirus (REOLYSIN®) are now underway to evaluate safety and efficacy in a wide variety of cancers, including ovarian, pancreatic, prostate, **colorectal**, non-small cell lung and breast cancers.

Reovirus and Metastatic Disease

Three factors seem to contribute to the possibility that metastatic disease would be susceptible to treatment with reovirus. First, reovirus appears to spread particularly easily to organs where metastasis is common, so a concentration of the drug can be built up in those regions of the body. Second, the cells that colonize a tumor to form the metastasis are believed to harbor genetic defects that provide a more accommodating environment for reovirus to colonize. Finally, a growing body of literature suggests Ras activation is required for metastasis to occur in the first place. At least five million new patients per year are expected to develop cancers with a Ras pathway involvement.

http://www.physiciansnews.com/2014/10/31/new-cancer-therapy-using-oncolytic-viruses-to-treat-metastatic-disease/

4. NSAIDS: Preventing Colon Cancer by Killing Mutated Intestinal Cells (Nov.8/14)

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) protect against the development of colorectal cancer by inducing cell suicide pathways in intestinal stem cells that carry a certain mutated and dysfunctional gene, according to a new study led by researchers. Scientists have long known from animal studies and clinical trials that use of NSAIDs, such as aspirin and ibuprofen, lowers the risk of developing intestinal polyps, which can transform into colon cancer. But they have not known why. "Our study identifies a biochemical mechanism that could explain how this preventive effect occurs," said lead researcher. "These findings could help us design new drugs to prevent colorectal cancer, which is the third leading cause of cancer-related deaths in the country." The research team performed experiments in animal models and examined tumor samples from patients who had taken NSAIDs and those who hadn't. They found that NSAIDs activate the so-called death receptor pathway, which selectively triggers a suicide program in intestinal stem cells that have a mutation in the APC gene that renders the cells dysfunctional. Healthy cells lack the mutation, so NSAIDs cause them no harm. In that manner, the drugs instigate the early auto-destruction of cells that could lead to precancerous polyps and tumors. "We want to use our new understanding of this mechanism as a starting point to design better drugs and effective cancer prevention strategies for those at high risk of colon cancer," Dr. Zhang said. "Ideally, we could harness the tumor-killing traits of NSAIDs and avoid possible side effects that can occur with their chronic use, such as gastrointestinal bleeding and ulcers."

Lin Zhang, Ph.D. et al. BID mediates selective killing of APC-deficient cells in intestinal tumor suppression by nonsteroidal antiinflammatory drugs.* PNAS, *November 2014 DOI*: *10.1073/pnas.1415178111

5. Results Released for Detection & Monitoring of KRAS Mutations in Circulating Tumor DNA of CRC Patients (Nov.20/14)

Trovagene announced clinical study results highlighting the Company's ability to detect and quantitate *KRAS* mutations in blood and urine samples from patients with advanced colorectal cancer. The data, generated using Trovagene's Precision Cancer Monitoring technology, show that quantitative changes of mutational signals in blood and urine are highly correlated and further establish the clinical applicability of a simple urine sample for cancer monitoring. Archived, matched plasma and urine samples (stored between 3-5 years prior to circulating tumor DNA [ctDNA] extraction) from 20 treatment naïve, advanced cancer patients with known *KRAS* mutations in tumor tissue were used in a retrospective setting for a blinded pilot study. Trovagene's platform technology, specifically its quantitative *KRAS* mutation assay, was used to analyze patient specimens and compare *KRAS* mutational status in urine, blood, and tissue samples. Results showed a highly correlated response. Of the blinded retrospective plasma ctDNA samples evaluated, 95% displayed the *KRAS* mutation concordant with tumor tissue, and for evaluable urine samples in the study, 92% displayed the *KRAS* mutation concordant with tumor tissue. The majority of patients in the study underwent surgery and received neo-adjuvant or adjuvant therapy, and serial monitoring of *KRAS* mutations using Trovagene's assay showed a clear correlation between blood and urine samples. An estimated analytical limit of detection of 7 copies per ~100,000 genome equivalents, or 0.0067% was observed in the study, demonstrating very high analytical sensitivity. Analysis of the association between the dynamics of mutant *KRAS* load, and changes in clinical status is ongoing. The

proven ability to monitor *KRAS* mutations in colorectal cancer is another step forward for their technology, and is also the first of several major cancer indications in which they anticipate to demonstrate clinical utility with their assay platform in the coming year.

http://www.prnewswire.com/news-releases/trovagene-releases-clinical-study-results-for-the-detection-and-monitoring-of-kras-mutations-in-circulating-tumor-dna-of-colorectal-cancer-patients-283333351.html

6. Can Metformin Prevent Colorectal Cancer in Diabetics? (Nov.25/14)

Studies have suggested that patients with type 2 diabetes may be at an increased risk for developing colorectal cancer (CRC); hyperinsulinemia, hyperglycemia, and chronic inflammation are thought to all contribute to carcinogenesis. Metformin, a biguanide, exerts it antihyperglycemic effects by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. Being that metformin is the most commonly prescribed medication for the treatment of type 2 diabetes, researchers sought to assess whether metformin use has an effect on the incidence of CRC in this patient population. A total of 8046 study participants were included in the analysis (2682 in the case group [diabetic patients with incident diagnosis of CRC]; 5364 individuals in the control group [diabetic patients without CRC diagnosis]); each group was 60% male, 40% female. In the case group, 36.6% of patients had metformin exposure, while 38.4% had metformin exposure in the control group. In this study, any metformin use led to a 15% reduction in the odds of CRC; after accounting for healthcare use, the effect was reduced to 12%. Reduction of risk was not significantly associated with metformin dose, duration or total exposure. Based on these results, researchers conclude that metformin appears to reduce the risk of developing CRC in patients with type 2 diabetes. However, more research needs to be done before metformin can be recommended as a colon cancer chemopreventive agent.

http://www.empr.com/can-metformin-prevent-colorectal-cancer-in-diabetic-patients/article/385272/

7. Biomarker Can Predict Benefit From Erbitux in CRC (Dec.26/14)

The biomarker **miR-31-3p** predicts cetuximab's (erbitux') efficacy in patients with all-*RAS* wild-type metastatic colorectal cancer, according to research. This is the first biomarker that pinpoints a patient population likely to experience detriment from cetuximab, according to post-hoc analyses from New EPOC Study. "The results of our study demonstrate that all-*RAS* wild-type metastatic colorectal cancer patients with high expression levels of miR-31-3p experience inferior progression-free survival when treated with the combination of chemotherapy plus cetuximab," said study co-author John Primrose, MD, a professor of surgery at the University of Southampton, in England, and the chief investigator for the study. The finding comes from post-hoc analysis of the Phase III trial, which had randomized patients to receive chemotherapy alone or chemotherapy plus cetuximab before and after resection of colorectal liver metastasis. The trial results had showed that *KRAS* exon 2 wild-type patients who received cetuximab along with standard chemotherapy and surgery for operable colorectal liver metastases had significantly reduced progression-free survival (PFS) compared with patients who did not receive cetuximab. Surprisingly, the greatest detriment was seen in patients with better prognoses and occurred even in those who responded to treatment, leaving investigators searching for a biological explanation. Dr. Primrose and his colleagues conducted the post-hoc analysis to look at biomarkers that could identify patients who benefit from treatments targeting epidermal growth factor receptor (EGFR). They focused on patients without a *KRAS* or *NRAS* mutation. The analysis revealed a strong relationship between **miR-31-3p** expression and patients' outcome after treatment with chemotherapy plus cetuximab. Among ***patients with high expression of miR-31-3p***, those who received the combination of chemotherapy plus cetuximab had just over one-third of the median PFS of patients treated with chemotherapy alone (13 vs. more than 35 months; hazard ratio, 2.7; 95% confidence interval, 1.1-6.4; *P*=0.02). However, when only patients with low levels of miR-31-3p were evaluated, PFS was no worse with the addition of cetuximab. In addition, the study identified a correlation between miR-31-3p expression in primary tumors and metastases in patients receiving chemotherapy alone but not in those receiving chemotherapy plus cetuximab, suggesting that **miR-31-3p** affects the EGFR pathway, Dr. Primrose said. "MiR-31-3p is a biomarker of harm from cetuximab, but we need to now understand the pathways involved and which genes are being regulated," he said. Co-investigator John Bridgewater, MD, a gastrointestinal oncologist at the University College London Hospitals, in London, England, said oncologists should take two key messages from the results. "Do not use EGFR inhibitors in a neoadjuvant setting, and there are complex molecular events about which we still understand very little." Investigators called for thorough testing of *RAS* status in all patients before giving an anti-EGFR antibody.

http://www.clinicaloncology.com/ViewArticle.aspx?d=Solid%2BTumors&d_id=148&i=December+2014&i_id=1135&a_id=28909

SURGICAL THERAPIES

8. Maximal Debulking Liver Resection as a Beneficial Treatment Strategy for Advanced and Aggressive Colorectal Liver Mets (Oct. 17/14)

Once upon a time, a survival benefit wass generally considered unobtainable following incomplete hepatic resection in patients with colorectal liver metastases. However, this question should be readdressed considering recent chemotherapy, often combining a monoclonal antibody directed against colorectal cancer with various classic and improved strategies. Researchers examined whether a survival benefit could be obtained from maximal reduction surgery for colorectal liver metastases. In this study, researchers retrospectively analyzed data from 165 patients with liver recurrence after hepatectomy for colorectal metastases. They hypothesized that recurrence soon after surgery, frequently involved metastases left behind during liver resection, resembling the situation after debulking hepatectomy. When patients were divided according to time of liver recurrence, patients with early recurrence had significantly poorer overall survival than those with later recurrence. However, patients with multiple bilobar metastases (n=77), having a greater likelihood of metastases left behind at hepatectomy, had similar survival whether recurrence was early or late. Response to chemotherapy before first hepatectomy was prognostically important for patients with early liver recurrence, as were number of recurrent tumors and status of extrahepatic disease. Researchers concluded that debulking surgery for multiple bilobar metastases may represent a treatment strategy with potential survival benefit, especially when initial metastases respond well to pre-hepatectomy chemotherapy.

Tanaka, Kuniya, et al., Maximal Debulking liver resection as a beneficial treatment strategy for advanced and aggressive colorectal liver metastases. Anticancer Research. October 2014 Vol 34. No.10; pp.5547-5554.

9. Predictors of Recurrence After a First Liver Resection for Colorectal Cancer Liver Mets (Dec.13/14)

Surgical resection is considered the standard therapy in the treatment of liver metastases from colorectal cancer (CRCLM); however, most patients experience tumour recurrence after curative hepatic resection. The objective of this study was to determine potential prognostic factors for tumour recurrence after an initial hepatectomy (liver resection) for CRCLM. A study population of 101 patients who had undergone a first curative hepatectomy for CRCLM was retrospectively analyzed. Selected biological tumour markers, and clinical and pathological features were then tested. Synchronous liver metastases occurred in 38 patients (37.6%) and 63 patients (62.3%) presented with metachronous liver metastases. In a median follow-up time of 68 months, recurrence was observed in 64 patients (63.3%). The 5-year cumulative risk of recurrence was 56.7%. The median survival after recurrence was 24.5 months (range 1 to 41 months) and 5-year cumulative overall survival was 31.8%. Of all variables tested, intra- and extrahepatic resectable disease, CEA levels ≥50 ng/mL and bilobar liver disease remained significant as predictors of recurrence in the multivariate analysis. Independent risk factors for recurrence after an initial hepatectomy for CRCLM, such as intra- and extrahepatic resectable disease, CEA levels ≥50 ng/mL and bilobar liver disease, can eventually help in making decisions in this very complex scenario.

http://www.wjso.com/content/12/1/391

10. Recurrence After Partial Hepatectomy for mCRC: Potentially Curative Role of Salvage Repeat Liver Resection (Jan.16/15)

According to this study, patients with recurrence after complete resection of colorectal liver metastases (CLM) are considered for repeat resection as a potential salvage therapy (PST). However, outcomes for this approach are not well defined. Researcherse sought to analyze the natural history of recurrence and PST in a large cohort of patients with long-term follow-up. Recurrence patterns, treatments, and outcomes in consecutive patients undergoing resection for colorectal liver metastases were analyzed retrospectively. PST was defined as repeat resection of all recurrent disease and effective salvage therapy (EST) as free of disease for 36 months after last PST. Factors associated with PST, EST, and outcomes were analyzed. Of 952 patients who underwent resection, 594 (62 %) experienced recurrence (median interval = 13 months). Initial recurrences involved liver (n = 157,26 %), lung (n = 167,28 %), multiple sites (n = 171,29 %), and other single sites (n = 99,17 %). PST was performed in 160 (27 %) of 594, most commonly with a single site of recurrence (n = 149). Young age, negative initial resection margin, initial tumor size <5 cm, and recurrence pattern were independently associated with PST. Thirty-six patients experienced EST (25 % of PSTs). Overall median survival was 61 and 43 months in those with recurrence. Median survival of patients undergoing PST was 87 months compared to 34 months for those who did not. Researchers concluded that recurrence is common after CLM resection, but 27 % of patients were able to undergo PST. Approximately one-quarter of these experienced EST and may be cured. PST is associated with long-term survival and possible cure, and therefore active surveillance after CLM resection is justified.

Butte, JM, et al., Recurrence after partial hepatectomy for metastatic colorectal cancer: potentially curative role of salvage repeat resection. Ann Surg Onc. 2015 Jan.9. Epub ahead of print.

SCREENING

11. Knowledge of Individual Risk Did Not Increase Colorectal Cancer Screening Adherence (Oct.20/14)

Receipt of individualized genetic and environmental risk assessments did not increase colorectal cancer screening rates, even among study participants whose assessments showed they were at elevated risk for the disease, according to results of a randomized, controlled trial. Researchers sought to evaluate whether a genetic and environmental risk assessment would improve screening adherence in 783 adults who were considered at average risk for colorectal cancer but were not regularly undergoing screening at baseline. Researchers assigned 514 participants to undergo the risk assessment, which included analyses for methylenetetrahydrofolate reductase polymorphisms and serum folate levels. The other 269 study participants received usual care. Overall, 34% of study participants underwent colorectal cancer screening within 6 months. Participants aged 70 to 79 years as well as those aged 60 to 69 years were more likely to undergo screening compared with those aged 50 to 59 years. Screening also was more likely among participants with greater knowledge about the process. Results showed participants who received the risk assessment were no more likely to undergo colorectal cancer screening than those who only received usual care. Researchers concluded that this large, randomized trial found no effect on colorectal screening rates in an average-risk population exposed to personalized genetic and environmental risk information.

Weinberg, David S., et al., Genetic and Environmental Risk Assessment and Colorectal Cancer Screening in an Average-Risk Population: A Randomized TrialRisk Assessment and Colorectal Cancer Screening. **Ann Intern Med.** ***2014;161(8):537-545. doi:10.7326/M14-0765***

12. New Evidence That Colonoscopy Reduces Cancer Risk (Oct.23/14)

Colonoscopy reduces cancer risk and mortality in patients with inflammatory bowel disease, according to the largest study of its kind. Initially, when colonoscopy was adopted and approved, there were no clear data that it reduced incidence or mortality from colorectal cancer, either in the general population or in those with inflammatory bowel disease. Current guidelines recommend that patients with inflammatory bowel disease undergo colonoscopy 8 to 10 years after their initial diagnosis, and every 2 to 3 years after the initial exam. Researchers identified 24,000 patients with ulcerative colitis or Crohn's disease from a multi-institutional electronic medical record cohort. Of these patients, 6823 had a validated diagnosis of inflammatory bowel disease. Investigators classified these patients into two groups: 2764 had a recent colonoscopy — in the 36 months before the diagnosis of colorectal cancer or before the end of the 8-year follow-up period; and 4059 did not. During the follow-up period, 154 patients developed colorectal cancer. Patients diagnosed with colorectal cancer were older, more likely to be male, and more likely to have a diagnosis of ulcerative colitis or primary sclerosing cholangitis. However, there was a clear association between colonoscopy and colorectal cancer. During the follow-up period, the incidence of colorectal cancer was significantly lower in those who had a recent colonoscopy than in those who had not.

American College of Gastroenterology (ACG) 2014 Annual Scientific Meeting: Abstract 9. Presented October 20, 2014.

http://www.medscape.com/viewarticle/833733

OTHER

13. The Risk of Colorectal Cancer in Patients with Ulcerative Colitis (Oct.16/14)

Ulcerative colitis increases the risk of developing dysplasia and colitis-associated cancer (CAC). The purpose of this study was to determine the risk factors as well as protective measures for disease burden, need for colectomy and the development of CAC in ulcerative colitis (UC) patients. A cohort of n = 434 UC patients was evaluated. Data analysis was performed. Mean patient age at UC diagnosis was 45.7 ± 15.1 years which manifested mainly as pancolitis (47 %) or left-sided colitis (45.2 %). CAC was detected in ten patients (2.3 %). UC disease duration was strongly associated with the risk of CAC; disease duration between 9 and 15 years. Despite the use of modern therapies for UC, CAC rates remain high. In the study, risk factors included disease duration while anti-inflammatory therapies reduced the risk. Effective control of the intestinal inflammation also reduced the disease burden as indicated by decreased risk of requiring colectomy, underscoring the need for sufficient surveillance and anti-inflammatory therapies.

Nowacki, TM, et al., The risk of colorectal cancer in patients with ulcerative colitis. Dig Dis Sci. 2014 Oct 4. Epub ahead of print.

14. Recent Increase in Incidence of Young-Onset Colorectal Cancer (Oct.20/14)

The incidence of young-onset colorectal cancer (CRC) is increasing, and the disease is more aggressive pathologically. Researchers examined the incidence and characteristics of young-onset (younger than 50 years) versus old-onset (50 years and older) CRC. The researchers found that from 2000 to 2011 the annual rate of increase was 1.4% for new cases of young-onset CRC, compared with a 3.1% annual decline in old-onset CRC. The rate of distant disease increased 3% annually, while localized or regional disease increased 1% annually among young-onset CRC. Young-onset CRC was more likely in males versus females and in blacks and Hispanics versus whites. Presentation was more likely at an advanced stage, higher grade, and in left-sided colon or rectum in young-onset disease. Larger tumor size, higher rates of lymph node positivity, perineural invasion, and positive surgical margins were seen for young-onset CRC. “Future research and efforts are ongoing to better understand the biology of young-onset CRC and to improve a CRC screening strategy for the younger patient population," the authors write.

***Zheng, Xi E., et al., Young-Onset colorectal cancer: a more aggressive disease on the rise. Program No.7. ACG 2014 Annual Scientific Meeting Abstracts.* Philadelphia, PA: American College of Gastroenterology.**

15. Moderate Delays in Cancer Treatment May Have No Effect on Patient Outcomes (Oct.22/14)

Delays between a patient presenting with symptoms of colorectal cancer to their GP and receiving treatment may have no impact on survival rates, according to this study. The study analyzed the time between a patient visiting their GP and receiving treatment for 958 patients between 1997 and 1998. The paper's authors hope the findings will help to reassure patients, and could feed into a wider discussion about current NHS waiting time targets. Of course GPs recognize that waiting for tests or treatment, particularly for cancer, causes anxiety and stress for patients and it is quite right that politicians, policy makers and staff in the health service have been focused on this 'time factor', and keeping it to a minimum by introducing waiting time targets. "However, it appears, certainly in cancer, that minimizing waiting times have acquired a biological significance that, in colorectal cancer anyway, may not be entirely warranted. "The assumption has been made, by policymakers and others that in patients with symptomatic colorectal cancer, the earliest possible diagnosis and treatment will improve survival from colorectal cancer. Our study shows this may not be the case. The study of 958 patients diagnosed between 1997-98 showed that delays of up to 20 weeks between presentation to a GP and treatment didn't lead to poorer survival." The findings contradict influential data by Danish researchers which concluded that delays of as little as 6 weeks between patients presenting to a GP with symptoms and receiving a diagnosis of colorectal cancer led to poorer survival. However, Dr Murchie and colleagues would argue that the CRUX (Comparing Rural and Urban Cancer Care) data examined as part of their research was more detailed. "The key thing the Danish team didn't have was information about the biology of the tumours. We had information on how aggressive the tumour was from the Scottish cancer registry, and we were able to control for this factor in our analysis, whilst they weren't. The team say there is an argument that the strict waiting time targets, and an emphasis on prioritizing patients with 'alarm symptoms', could be having negative effects on some patients. "Because delays are viewed as critical, patients that present with 'alarm' symptoms of cancer or possible cancer, such as rectal bleeding, are prioritized for rapid investigation and treatment. "The vast majority of those patients won't have cancer, and aren't necessarily more likely to have cancer than people who present with vaguer symptoms such as an altered bowel habit. However the current system means that even if a GP strongly suspects someone with vaguer symptoms is more likely to actually have cancer, they probably won't get seen ahead of someone with alarm symptoms. "In addition, there is a risk that the current targets for treating people that exist within the NHS mean that opportunities to prepare people fully for the most appropriate treatment are being missed." "The team feel the results should encourage policy makers to look again at the way waiting time targets are set. "The reassuring message we've got for patients diagnosed with CRC is that there is no good evidence to suggest that moderate delays between them presenting to their GP and being diagnosed and treated worsens their outlook. That's not to say that every step should not be taken to ensure patients receive their diagnosis and treatment as promptly as possible, and as appropriate. "Going forward we think this data feeds into the wider conversations about waiting time targets. It could be argued that relaxing waiting time targets longer could reintroduce the ability of GPs to put forward timely investigation diagnosis and treatment for patients that the GP suspects may have cancer, but don't fit the 'urgent suspected cancer' guidelines. It could also enable those with vaguer symptoms to be prioritized over those with alarm symptoms, if the GP feels it appropriate."

Munchie, P. et al., Time from first presentation in primary care to treatment of symptomatic colorectal cancer: effect on disease stage and survival." British Journal of Cancer 111, 461-469 (29 July 2014) | DOI: 10.1038/bjc.2014.352

16. 62% of Colorectal Cancer Patients Report Financial Burden From Treatment (Oct.24/14)

Nearly two-thirds of patients treated for colorectal cancer reported some measure of financial burden due to their treatment. The burden was greatest among patients who received chemotherapy and among younger patients who worked in low-paying jobs. The study surveyed 956 patients who had been treated

for stage 3 colorectal cancer. Among this group, chemotherapy is known to increase survival by up to 20 percent and is routinely recommended following surgery. The financial burden was higher in patients who received chemotherapy -- a potentially lifesaving treatment. “To ensure that patients can receive all recommended care, we need to recognize the financial burden of cancer and identify patients at risk for financial concerns. younger, working low-income patients were especially likely to face financial burden. These are people who may not be able to afford to take time off from their jobs to get recommended cancer care, including chemotherapy," lead researcher Veenstra adds. Patients were asked to answer a seven-question survey that asked whether they had used savings, borrowed money, skipped bill payments or cut back on items such as food, clothing or recreational activities because of their cancer treatment. Overall, 38 percent did not indicate financial burden based on the seven questions. Of the remaining 62 percent:

• 29 percent indicated 1-2 areas of burden

• 23 percent indicated 3-4 areas of burden

• 9 percent indicated 5 or more burdens.

Nearly half of patients noted that they cut down on expenses in general because of their cancer treatment. Patients who had chemotherapy were significantly more likely to select each item of financial burden. "It's important to note that this financial burden is experienced on top of all that patients are going through with the cancer itself. The financial burden hits hard," says senior study author Arden M. Morris, M.D., M.P.H., chief of colorectal surgery at the University of Michigan Medical School and associate professor of health behavior and health education at the School of Public Health. The researchers urge policy changes to job support measures such as mandatory paid sick leave or disability benefits. They also recommend support for copays, parking and transportation. In addition, patients should speak to their doctor about financial concerns, and doctors should be aware of the financial burden on patients. "It's important to start the dialog between patients and doctors. Some financial supports currently exist that may benefit patients if they're aware. It may not be enough to fully cover their financial burden, but it could help," says Morris, who is also a member of the University of Michigan Center for Healthcare Outcomes and Policy and the Cancer Surveillance and Outcomes Research Team.

Veenstra, Christine, et al A Composite Measure of Personal Financial Burden Among Patients With Stage III Colorectal Cancer*. Medical Care*, 2014; 52 (11): 957 DOI: 10.1097/MLR.0000000000000241

NUTRITION & HEALTHY LIFESTYLE

17. Calcium, Vitamin D, Dairy Products, and Colorectal Cancer (Oct.20/14)

Diet and lifestyle changes may play an important role in cancer pathogenesis. Yang and fellow American Cancer Society investigators analyzed the role of calcium, vitamin D, and dairy product intake before and after diagnosis of nonmetastatic colorectal cancer. The study population comprised 2284 participants in a prospective cohort study. Diet and modifiable lifestyle factors are important issues for survivors of localized colorectal cancer. Unfortunately, randomized trials in this setting are difficult to conduct, require prolonged follow-up, and may not be able to control for all lifestyle factors. Therefore, data from well-conducted prospective cohort studies may be good enough to make recommendations to patients. This study suggests that increased milk and calcium intake is associated with improved outcomes. Limitations include the primarily white study population with known higher rates of lactase persistence; in addition, the lack of association with vitamin D intake is inconsistent with prior reports. Increased milk and calcium intake, along with reduced red meat intake and regular exercise, can be discussion points for survivors of colorectal cancer interested in modifiable lifestyle risk factors.

Zgaga L, et al. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. J Clin Oncol. 2014;32:2430-2439.

18. Mediterranean Diet Linked to Lower Colorectal Cancer (Oct.20/14)

The western diet has been linked to a higher risk of colorectal cancer. A new study suggests that eating a Paleolithic diet or Mediterranean diet may lower the risk significantly. Researchers compared the diets of 564 men and women with colorectal cancer with the diet used by 1202 controls who did not have the disease and found greater adherence to either diet was associated with significantly reduced risk for colorectal cancer. When the cases were compared with 535 community controls, a similar association was found. Specifically, those in the highest quintiles of the Paleolithic and Mediterranean diet scores relative to the lowest quintiles were 29% and 26% less likely to be diagnosed with colorectal cancer respectively. When community controls were used, those in highest quintiles of the Paleolithic and Mediterranean diet scores were at 16% and 23% reduced risk of colorectal cancer respectively.

Whalen KA, et al., Paleolithic and Mediterranean diet pattern scores and risk of incident, sporadic colorectal adenomas. Am J Epidemiol. 2014 Oct. 17.

19. Prehabilitation Before Colon Cancer Surgery may Aid Recovery (Oct.27/14)

Following a conditioning, nutritional, and relaxation program before surgery is more helpful than waiting until after surgery to rehabilitate, suggests a new study. Colorectal cancer patients who participated in a "prehabilitation" program before surgery recovered more quickly than those who only did traditional rehabilitation afterward, according to research. In the randomized controlled trial, patients assigned to a program of exercise, nutritional counseling with protein supplementation and relaxation exercises were able to walk significantly farther two months after surgery than those who did not participate in prehabilitation. Both groups were prescribed traditional rehabilitation after surgery. "Prehabilitation prepares patients to withstand the stress of surgery so they are able to recover faster and function better after the procedure," said Francesco Carli, M.D., M.Phil., lead author of the study and professor of anesthesia at McGill University Health Centre, Montreal. "Pre-surgery conditioning helps patients take an active role in their own recovery. We believe instituting prehabilitation before surgery when possible could improve health and recovery and reduce costs." In the study, 38 patients participated in the prehabilitation program, while 39 were assigned to the rehabilitation-only group. The prehabilitation prescription included:

- 50 minutes of home-based unsupervised exercise at least three days a week, including aerobic and resistance training,
- a dietitian-created individualized nutrition program and whey protein supplementation, and
- a visit with a psychologist to learn how to reduce anxiety through relaxation exercises based on imagery and visualization and breathing exercises.

The average length of prehabilitation was 24.5 days. After surgery, patients in both groups followed the same rehabilitation program. Researchers measured how far patients could walk in six minutes at the start of the study (before any intervention) and there was no significant difference between the groups: 421 meters on average in the prehabilitation group, and 425 meters on average in the rehabilitation-only group. Researchers had patients repeat the walking test right before surgery and at four and eight weeks after surgery. Those in the prehabilitation group improved significantly during the pre-surgery period, walking an average of 25.2 meters farther than they had at the start of the study, while those in the rehabilitation-only group declined, walking an average of 16.4 meters less. Eight weeks after surgery, prehabilitation patients walked an average of 23.2 meters farther than at the start of the study, while rehabilitation-only patients continued to lose ground, walking an average of 21.8 meters less.

Carli, Francesco, et al., . Prehabilitation versus Rehabilitation. **Anesthesiology*, 2014; 121 (5): 937 DOI: 10.1097/ALN.0000000000000393***

20. Dietary Supplements May Affect CRC Risk (Nov.7/14)

Use of dietary supplements is increasing in countries where colorectal cancer (CRC) is present, but is there an association between supplement use and CRC risk? A new study in the *International Journal of Cancer* presents a systematic review and meta-analysis of 24 prospective cohort studies on dietary supplement use and CRC risk using research published up to January 2013. A statistically significant inverse relationship was observed between use of multivitamin and calcium supplements and CRC risk; in six studies, an increase of 100mg/day of supplemental calcium was linked with a significantly reduced risk of CRC. For vitamins A, C, D, and E, plus garlic and folic acid, either no associations or inconsistent results were observed (such as from dietary vs. supplemental sources). However, the potential role of lifestyle factors in CRC risk and methodological variables in the assessed research do limit these study results. According to the researchers, in the future, research should take into account recall of supplement use, duration of supplement use, type of supplement clearly defined, seasonal influences, and lifestyle factors for improved results.

Renate, C., et al., Dietary supplement use and colorectal cancer risk: A systematic review and meta-analyses of prospective cohort studies. Intl J of Cancer. Article first published online: 11 NOV 2014. DOI: 10.1002/ijc.29277.

21. Too Much TV and Survival Odds After Colon Cancer (Dec.8/14)

Watching too much television may lower your chances of survival after colon cancer, new research suggests. The take-away message from the study is that both minimizing TV viewing, to less than two hours per day, and increasing exercise, to four-plus hours per week, were associated with lower mortality risk among colorectal cancer survivors. While the study showed an association between television watching, exercising and survival odds among colon cancer patients, it did not prove a cause-and-effect link. To explore the impact of lifestyle on colon cancer survival, the study authors sifted through data that had been collected by the U.S. National Institutes of Health for an earlier study. The initial investigation had included more than 566,000 men and women between the ages of 50 and 71, all of whom had completed an initial health and lifestyle questionnaire at some point between 1995 and 1996. All were asked to indicate the degree to which they had routinely participated in moderate to vigorous "leisure-time activity" on a weekly basis over the past decade. Activities included swimming, biking, golf, tennis, dancing, fast-walking, jogging, aerobic exercise and/or heavy gardening. The new analysis honed in on the nearly 3,800 participants who went on to be diagnosed with colon cancer. On average, the diagnoses

had occurred approximately five years following completion of the initial survey. By stacking pre-diagnosis exercise habits up against cancer survival information, the researchers determined that colon cancer patients who had seven or more hours of weekly leisure activity before their diagnosis showed a 20 percent lower risk of dying -- for any reason -- than those who had engaged in no leisure activity whatsoever. And after analyzing a follow-up survey completed between 2004 and 2005 by roughly 1,800 of the original 3,800 colon cancer patients, the team found that those who engaged in seven or more hours of weekly leisure activity post-diagnosis faced a 31 percent lower risk of dying from any cause, regardless of their activity levels before diagnosis. The study team also found that those patients who routinely watched no more than two hours of TV per week before diagnosis faced a 22 percent lower risk of dying from any cause than those who watched five or more hours per week. Television viewing was chosen as a stand-in for sedentary behavior because it is the most prevalent leisure-time sedentary behavior. The research team found a lower mortality risk among those who watched less TV post-diagnosis, although it was not deemed statistically significant. On the more specific question of how exercise habits and television viewing routines might affect the risk of dying from colon cancer, researchers said the team could not draw any firm conclusions. "We looked at both all-cause mortality and colorectal cancer-specific mortality in these analyses" , "[And] the risk of dying from colorectal cancer was higher among the individuals who watched more TV compared to those who watched less than two hours per day, but the associations were not statistically significant." The team nevertheless concluded that when dealing with colon cancer patients, doctors may want to stress the potential benefits associated with increased activity on the one hand, and minimal television watching on the other. Dr. Andrew Chan, an associate professor in the department of medicine at Harvard Medical School, said the findings highlight the strong link between lifestyle choices and health. "We are becoming more and more aware of the importance of lifestyle in really determining how someone is going to do after they've been diagnosed with cancer," he noted. "And it's time that patients come to understand that, in general, being more physically active is important to maintaining one's health." "Now, of course, lifestyle is important no matter who you are, even for individuals who don't have a history of cancer," added Chan, who is an associate professor of medicine and gastroenterology at Massachusetts General Hospital in Boston. "But certainly for cancer survivors specifically, this study drives home the point that an active lifestyle can be critical, both for maintaining overall health and preventing the recurrence of disease."

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http://www.nlm.nih.gov/medlineplus/news/fullstory_149849.html