

COLORECTAL CANCER RESEARCH Month Ending April 8th, 2011



The following colorectal cancer research update extends from March 19th, 2011 – April 8th, 2011 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. **KRAS Mutations Match in Primary Tumour and Liver Mets** (Mar. 21/11)

If there is a KRAS mutation in the primary colon or rectal tumor, there is almost always a matching mutation when that tumor spreads to the liver. Researchers in the Netherlands tested both tumors for KRAS mutations in over 300 patients whose cancer had spread to their livers. They found about a third of patients had KRAS mutations and KRAS status matched in 96% of the cases, making it possible to test either tumor to make decisions about treatment with Erbitux® (cetuximab) or Vectibix® (panitumumab) Out of 305 tumors:

- 108 had a KRAS mutation in either the primary colorectal or metastatic liver tumor (35.4%)
- KRAS mutations didn't match in 11 of the 108 (3.6%)
- Of those:
 - 5 had a wild-type (normal) primary and KRAS mutation in the liver metastasis
 - 1 had a KRAS mutated primary and the liver met was wild-type
 - 5 had different KRAS mutations in the primary and liver tumors.

Researchers in the Netherlands concluded: "We observed a high concordance of KRAS mutation status of 96.4% between primary colorectal tumours and their corresponding liver metastases. In only six patients (2.0%), the discordance was clinically relevant. In this largest and most homogenous study to date, we conclude that both primary tumours and liver metastases can be used for KRAS mutation analysis".

The KRAS gene provides instructions for making a protein called K-Ras that is involved primarily in regulating cell division. Through a process known as signal transduction, the protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide or to mature and take on specialized functions (differentiate).

*The KRAS gene belongs to a class of genes known as oncogenes. When **mutated**, oncogenes have the potential to cause normal cells to become cancerous. The KRAS gene produces a protein that plays an important role in cell division, cell differentiation, and the self-destruction of cells (apoptosis). In colorectal cancer, mutations in the *kras* gene prohibit metastatic colorectal cancer patients from accessing anti-egfr therapies such as vectibix and erbitux because evidence shows that these therapies are not effective when administered to patients who have an identified *kras* mutation. (<http://ghr.nlm.nih.gov/gene/KRAS>)*

Knign, N, et al., Kras mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. British J of Cancer; 104, pp. 1020-1026.

2. Administering Folfox 6 with Avastin in Non-optimally resectable Liver Mets (Mar. 29/11)

Researchers maintain that in patients with colorectal liver metastases (CLM), a complete resection (R0) significantly improves overall survival (OS). In this study, investigators present the results of a phase II trial of FOLFOX6+bevacizumab (avastin) in patients with non-optimally resectable CLM. Patients received six cycles of FOLFOX6 + five of bevacizumab. Patients who still did not qualify for surgery received six additional cycles of each. A PET-CT was performed at baseline and again within 1 month after initiating treatment. From September 2005 to July 2009, 21 patients were enrolled. An objective response (OR) was documented in 12 cases. Thirteen patients underwent radical surgery (61.9%). Six patients (46.1%) experienced minor postsurgical complications. After a median 38.8-month follow-up, the median OS was 22.5 months. Investigators noted that those patients who achieved at least 1 unit reduction in Standard uptake value (SUV)max on PET-CT had longer progression-free survival (PFS – time before disease got worse - 22 v.s. 14 months). Researchers therefore concluded that FOLFOX6 + bevacizumab does not increase postsurgical complications and yields high rates of resectability. Early changes in PET-CT values appear to be predictive of longer PFS.

Bertolini, F. et al., Folfox6 and bevacizumab in non-optimally resectable liver metastases from colorectal cancer. British J of Cancer (2011) 104, pp. 1079-1084

3. Effect of Simvastatin on Erbitux Resistance with KRAS Mutations (Mar. 29/11)

Metastatic colorectal cancer (CRC) patients with KRAS mutations are resistant to treatment with cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor. Statins have reported antitumor activity, but it is unknown whether a well known statin – simvastatin - can reverse cetuximab resistance in KRAS mutant CRC. In the study, human CRC cells with KRAS mutations or with BRAF were used to test the effect of cetuximab, simvastatin, and cetuximab plus simvastatin on cell proliferation and cell death. Addition of simvastatin to cetuximab reduced cell proliferation of KRAS mutant but not of BRAF mutant CRC cells. Treatment of KRAS mutant cells with simvastatin reduced BRAF activity and induced cell death (apoptosis). Treatment with cetuximab and simvastatin reduced the growth of tumors originating from KRAS mutant cells compared with cetuximab; treatment with cetuximab alone or in combination with simvastatin had no effect on the growth of BRAF mutant tumors. Researchers concluded that simvastatin may overcome cetuximab resistance in colon cancer cells with KRAS mutations by inducing cell death (apoptosis). ***Please note that this is an early and limited study which requires additional testing in human subjects to confirm the effect of simvastatin administered in combination with cetuximab in KRAS mutant patients.

*Lee, Jeeyun, et al., Effect of simvastatin on cetuximab resistance in human colorectal cancer with *kras* mutations. J of National Cancer Institute. First published online: March 11, 2011.*

4. Addressing the Hypersensitivity to Cold Caused by Oxaliplatin (Apr.4/11)

For patients receiving chemotherapy treatment that consists of oxaliplatin, a common side effect is hypersensitivity to cold. It happens in approximately 95% of patients, wherein the drug causes increased sensitivity to cool or cold temperatures from the first infusions, resulting in tingling in the extremities. To help remedy the unwanted side effect, patients will put gloves on before opening the fridge, avoid the refrigerated section in supermarkets and avoid coming in contact with cool temperatures or objects. This

known side effect is so uncomfortable that some patients reduce or even stop their chemotherapy. No preventative treatment is currently available. In this study however, a team of researchers have shown that, as is the case in humans, administration of oxaliplatin in mice increases sensitivity to cold. A molecule already marketed in France for the treatment of angina has been shown to restore the excitation thresholds of cold-sensitive neurons (nerve cells) to normal levels. The molecule is known as Ivabradine and it was not only able to restore the normal excitation threshold of cold-activated neurons, but it did not affect other populations of sensory neurons, such as touch receptors. This molecule, already used in the clinic to treat angina, could be a promising preventative treatment against the acute neurotoxicity induced by oxaliplatin in colorectal cancer patients. Additional testing is required before the agent is administered as a prophylactic in the prevention of oxaliplatin-induced cold hypersensitivity.

Descoeur, Juliette, et al., Oxaliplatin-induced cold hypersensitivity is due to remodeling of ion channel expression in nociceptors. EMBO Molecular Medicine, online publication, March 23, 2011.

5. Venlafaxine for the Prevention of Oxaliplatin-Induced Neuropathy (Apr.5/11)

The most serious side effects limiting use of the chemotherapeutic agent oxaliplatin are acute sensory neuropathy, which is typically triggered by cold exposure, and cumulative, chronic peripheral neuropathy. Finding strategies that improve neurotoxicity without affecting the anti-tumor activity of oxaliplatin is an important goal, and various approaches have been tried. In a previous small study, (Durand et al) investigators found that a 50-mg dose of oral **venlafaxine** protected against acute neurosensory toxicity in patients receiving an oxaliplatin infusion. To explore this finding further, the researchers conducted a randomized, double-blind, placebo-controlled phase III trial to evaluate the efficacy of venlafaxine in managing oxaliplatin-induced acute neurotoxicity. From October 2005 to May 2008, the study enrolled eligible adult patients with cancer who reported acute neurotoxicity following biweekly treatment with oxaliplatin. A total of 48 patients were included in the study; 72.9% of patients had colorectal cancer. At inclusion, patients had similar oxaliplatin exposure and similar intensity of symptoms. The symptoms shared by the patients included burning, cold-evoked pain, pins and needles. After baseline assessment, patients were randomized to treatment groups.

- **Group A** (n = 24) received venlafaxine immediate release (50 mg) 1 hour prior to oxaliplatin infusion (day 1 of chemotherapy), followed by venlafaxine extended release (37.5 mg twice daily) on day 2 through day 11.
- **Group B** (n = 24) received placebo 1 hour prior to oxaliplatin infusion, followed by placebo (twice daily) on day 2 through day 11. Venlafaxine and placebo were withheld on days 12 and 13. Study treatment resumed on day 14 (day 1 of the next cycle), following the same protocol as for cycle 1, and continued as long as oxaliplatin therapy continued.

During study treatment, on day 1 through day 5 of chemotherapy, patients rated their symptoms over the previous 12 hours, rated their functional impairment (0–10), and estimated relief of symptoms experienced with treatment (0%–100%). Neurosensory symptoms were reevaluated 3 months after discontinuing treatment. The primary endpoint was the percentage of patients with 100% relief of acute neuropathy. Secondary endpoints were the percentage of responders (patients with ≥ 50% relief of symptoms), and percentage of patients with grade 0 and grade 3 neuropathy at 3 months. Of 48 patients randomized, 20 from group A and 22 from group B were analyzed for neurotoxicity. The data revealed the following:

- that **a significantly greater number of patients receiving venlafaxine experienced 100% relief of acute neuropathy (31.3% vs 5.3%)**
- **the responder rate also was significantly greater with venlafaxine (68.8% vs 26.3%)**
- **Additionally, venlafaxine improved pins and needles and functional status and was associated with a lower rate of grade 3 neuropathy (0% vs 33.3%)**

Venlafaxine caused no grade 3 or 4 adverse events. The investigators maintained that although small, this phase III trial provides important evidence on the clinical activity of venlafaxine in preventing oxaliplatin-induced acute neurotoxicity. Larger prospective trials are needed to confirm the efficacy of complementary treatment with venlafaxine in ameliorating this often treatment-limiting side effect of oxaliplatin.

Durand, JP, et al., Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of effox, a randomized, double blind placebo-controlled phase III trial. Annals of Oncol. 2011 March 22; epub ahead of print.

6. Stronger Chemo + Immune Boost May Help Metastatic Colorectal Cancer Patients (Apr. 7/11)

By giving more intensive chemotherapy along with drugs designed to boost the body's own immune system, researchers were able to roughly double survival time for patients with advanced, metastatic colorectal cancer compared to patients receiving standard chemotherapy alone. In fact, the trial, whose results are being presented at the annual meeting of the American Association for Cancer Research in Orlando, was stopped early because of the promising findings. "With this study, we have produced for the first time strong proof-of-concept that chemo-immunotherapy may be active and more efficacious than standard [chemotherapy] in metastatic colon cancer patients," said study lead author Dr. Pierpaolo Correale. The standard of care right now for patients with colorectal cancer that has spread to other regions is to use one of two dual-drug combinations of chemotherapy alone, or use them alongside a

newly developed monoclonal antibody treatment such as Avastin (bevacizumab) or Erbitux (cetuximab). These approaches can boost overall survival to about 20 to 22 months. For this study, the research team randomized 130 patients to receive either chemotherapy alone (with a regimen known as FOLFOX) or to receive FOLFOX plus drugs to ramp up the immune system (this regimen is known as **GOLFIG**). The chemo/immune boost approach involves first giving patients the chemo gemcitabine plus standard FOLFOX chemotherapy (oxaliplatin, levofolinic acid and 5-FU/**GOLF**) that targets and kills the cancer cells in a number of ways -- all the while sending off signals alerting the immune system to the cancer. This is then followed up with the administration of signaling molecules called **cytokines** that spur key immune cells into action. Another immune-boosting cancer drug, called **aldesleukine**, is also given to help boost the population of immune cells targeted against tumor cells. At the time of data collection, the patients treated with this approach have survived an average 16.5 months without a relapse, compared with just 7.5 months in the chemo-only group. But the study began in 2005, before the advent of drugs like Avastin or Erbitux, meaning that investigators do not yet know if **GOLFIG** would outperform regimens that include those medications. This needs to be looked at. On the other hand, many patients do not see a benefit from biological agents such as Erbitux or Avastin because they have the wrong genetic profile. "Essentially, we have a very problematic subset of patients with metastatic colorectal cancer which are limited to two lines of chemotherapy and [perhaps] one biological agent," said Dr. Igor Astsaturov, assistant professor of medical oncology at the Fox Chase Cancer Center in Philadelphia. "For those patients, which are about one-third of the overall patient population, this [new finding] will be particularly welcome news," Astsaturov said, while adding the caution that the results are still preliminary. However, clinical use of the protocol may be delayed further by the fact that "there is no direct commercial interest of pharmaceutical companies," noted Correale, who is nevertheless planning larger trials. The costs associated with GOLFIG, he added, are "four-to-five times lower than that produced by the current use of Avastin or Erbitux with apparently similar therapeutic results." Because this study was presented at a medical meeting, the findings should be viewed as preliminary until they are published in a peer-reviewed journal.

Correale, Pierpaolo, et al., American Association for Cancer Research (2011, April 6). GOLFIG increased progression-free survival in colorectal cancer patients. Abstract #5511.

SURGICAL THERAPIES

7. Liver Resection in the Elderly (Mar. 29/11)

With the aging population, more elderly patients are being considered for hepatic resection (liver surgery). Researchers investigated whether advanced age was associated with higher rate and severity of postoperative complications in this study. A total of 75 patients aged ≥ 70 years (group E) were matched with 75 patients aged < 70 years (group Y) by the extent of liver resection and by operative indications. The primary outcome measures that were determined were rates and severity of complications. Secondary outcome measures were length of hospital stay and discharge destination. Male-to-female ratio was 43:32 in both groups. Overall complication rates were 44 and 33.3% in group E and Y, respectively. Researchers reported that there was no mortality in both groups. The only postoperative age-related morbidity was confusion in the elderly. There was no difference in the rates of severe complications between group E and group Y (16 vs. 14.7%). Median lengths of hospital stay were 7 and 6 days, respectively. Nineteen percent and 1% of patients in group E and group Y were discharged to rehabilitation facilities, respectively. The results showed that preoperative systemic chemotherapy and longer operative time were associated with higher morbidity (complications) in the elderly. Researchers concluded that liver resection can be performed in patients aged ≥ 70 years as safely as in younger patients. Duration and timing of systemic chemotherapy before liver resection should be optimized to minimize postoperative complications.

Steel, J. et al., Safety of liver resection in the elderly: how important is age? Ann Surg Oncol. 2011 Mar 1; 18(4): pp. 1088-1095

8. Outcomes Are Affected by Recurrence Patterns After Liver Mets Surgery (Mar. 29/11)

Despite improvements in surgery and chemotherapy, most patients develop recurrence after hepatectomy (liver surgery) for metastatic colorectal cancer. Data are lacking on the effect of these patterns on outcome. Hence, a retrospective review of a hepatobiliary database was performed. Pattern and timing of recurrence and outcome after recurrence were analyzed. From January 1997 through May 2003, a total of 733 patients underwent hepatectomy for colorectal metastases. Of these, 637 patients (87%) were included in the analysis, and in 393 patients (62%), recurrence was documented at the time of last follow-up. Initial recurrence patterns included the following:

- liver only in 120 patients (31%),
- lung only in 107 (27%),
- other single sites in 49 (12%),
- and multiple sites in 117 (30%).

Recurrence occurred within 2 years of hepatectomy in 75% of patients and after 3 years in 11%. Margins at hepatectomy, recurrence pattern, resected recurrence, and disease-free interval from time of colectomy (colon surgery) to hepatic metastasis and from time of hepatectomy to recurrence were

independently associated with survival as measured from the time of recurrence. ***Recurrence in the lung, resected recurrence, and time to recurrence after hepatectomy were associated with prolonged survival as measured from the time of hepatectomy and the time of recurrence.***

Researchers concluded that the timing and pattern of recurrence after hepatic resection for metastatic colorectal cancer are important predictors of long-term survival.

D'Angelica, M., et al., Effect of outcome of recurrence patterns after hepatectomy for colorectal metastases. Ann Surg Oncol. 2011 March 1; 18(4): pp. 1096-1103.

9. Laparoscopic Colorectal Surgery in the Elderly (Mar. 30/11)

The aim of this study was to review the impact of age (≥ 75 years) on the short-term outcomes of laparoscopic colorectal surgery. Three hundred seventy-nine patients under 70 years of age and 91 patients 75 years and older were analyzed. Outcome measures were two-fold: postoperative complications and 30-day mortality. According to the investigators, there was no difference in the occurrence of postoperative complications between the younger and older patients. The data analyzed revealed that patient age was not a risk factor of major complications. Although additional analysis revealed that older age had a greater propensity for 30-day mortality wherein specifically long operative time was an independent predictor of 30-day mortality and not age per se. The researchers concluded that age is not an independent predictor of morbidity and mortality in laparoscopic colorectal cancer surgery.

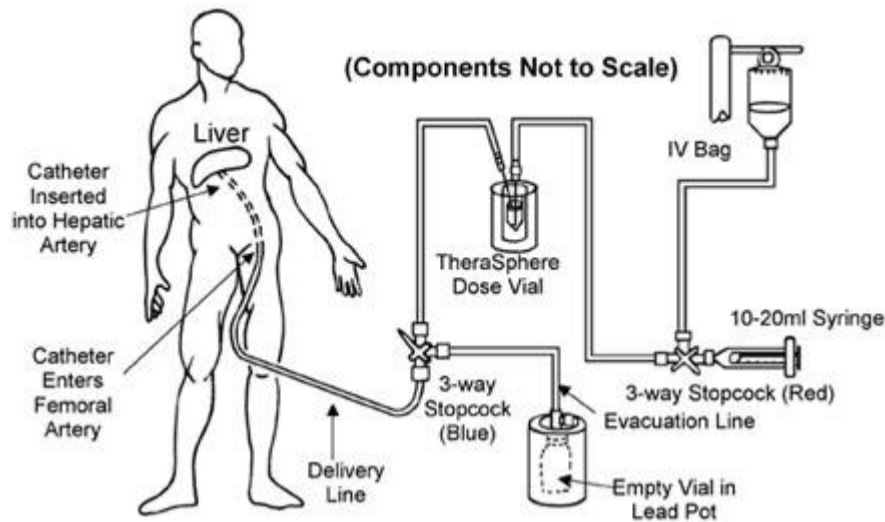
Tan, Kok-Yang, et al., Laparoscopic colorectal surgery in elderly patients: a case-control study of 15 years of experience. Amer J of Surgery. Vol. 201, Issue 4: pp. 531-536

RADIATION / INTERVENTIONAL RADIOLOGY

10. Phase III Clinical Trial Using Theraspheres for Liver Mets (Mar.23/11)

Approval has been granted to the company Nordion to conduct a Phase III clinical trial for TheraSphere® to evaluate the safety and effectiveness of TheraSphere treatment in colorectal cancer patients whose disease has metastasized to the liver. This randomized Phase III clinical trial, known as the EPOCH study, will take place at up to 30 sites worldwide, with a target enrolment of approximately 350 patients. The Principal Investigator is Dr. Mary Mulcahy of Northwestern University in Chicago, IL. The trial will examine a number of safety and efficacy endpoints in patients who have developed liver tumours from colorectal cancer and who have failed first-line chemotherapy. Participants in the treatment group will receive both TheraSphere and second-line chemotherapy, while patients in the control group will only receive the chemotherapy regimen. The goal is to investigate whether TheraSphere used in combination with chemotherapy can offer patient outcome advantages that are superior to those of chemotherapy alone. The EPOCH trial will help determine TheraSphere's clinical utility in combination with chemotherapy, and further advance our knowledge about TheraSphere's potential benefit to patients with liver metastases from colorectal cancer.

TheraSphere is a liver cancer therapy that consists of millions of small glass beads (20 to 30 micrometers in diameter) containing radioactive yttrium-90 (Y-90). The product is injected by physicians into the main artery of the patient's liver through a catheter, which allows the treatment to be delivered directly to the tumour via blood vessels. TheraSphere is cleared by the U.S Food and Drug Administration (FDA) under a Humanitarian Device Exemption (HDE). HDE approvals are based on demonstrated safety and probable clinical benefit. However, effectiveness of the indication for use has not been established. TheraSphere treatment can generally be administered on an outpatient basis and does not usually require an overnight hospital stay. TheraSphere is used to treat patients with unresectable hepatocellular carcinoma (HCC) and can be used as a bridge to surgery or transplantation in these patients. It can also be used to treat primary liver cancer patients with portal vein thrombosis. Common side effects include mild to moderate fatigue, pain and nausea for about a week. Physicians describe these symptoms as similar to those of the flu. Some patients experience some loss of appetite and temporary changes in several blood tests.



TheraSphere consists of millions of radioactive microscopic glass spheres, which are infused into the arteries that feed liver tumors. The interventional radiologist makes a small incision in the groin and places a catheter into the femoral artery under x-ray guidance. This catheter or tube is advanced up into the hepatic artery that feeds the cancerous tumor. A treatment plan is developed by the nuclear medicine physician to infuse the radioactive material in the spheres, Yttrium-90, directly into the liver to target the tumors and spare healthy liver tissue and surrounding normal structures. The beta radiation from the Yttrium-90 provides a local therapeutic effect. For details on rare or more severe side effects, please refer to the TheraSphere package insert at www.nordion.com/therasphere.

<http://www.digitaljournal.com/pr/256461>

11. Liver Mets Respond to Radiation Microspheres (Mar.30/11)

Targeted radiation delivered intra-arterially to liver metastases among patients with metastatic colorectal cancer, neuroendocrine tumors, or other metastatic cancers appears to halt progression with little toxicity, according to results of this open-label phase II study. Treatment with microscopic pellets of yttrium-90 (Y-90, TheraSphere) yielded a partial response or stable disease in 69.2% of these patients who failed prior chemotherapy regimens. While the experimental therapy didn't eradicate any tumors, no severe adverse effects were seen in more than 1% of patients with intra-arterial Y-90. Mild fatigue and nausea were the most common side effects of the treatment, with grade 3 events limited to a 6% rate of pain and of elevated alkaline phosphatase levels indicating liver function problems. Intra-arterial delivery of radiation -- akin to seed radiation implants for prostate cancer, but smaller and higher dose -- could change the standard of care for liver tumors, according to the principal investigator. These sorts of very high level, very potent therapies can be performed on an outpatient basis. The group conducted a single-arm, prospective, open-label trial in 151 patients with unresectable liver metastases refractory to or inappropriate for other systemic or targeted therapies. Most of these patients had primary colorectal (n=61) or neuroendocrine (n=44) cancers. In the month prior to treatment, patients got imaging to map out the volume of tumor that would need to be treated and determined dose and catheterization route for delivery. Patients got a total of 120 Gy of radiation in one or two doses from the glass encased microspheres, and investigators reported that the radiation did not travel beyond the liver in any cases. The median progression-free survival (time before the cancer got worse) was 2.8 months among colorectal cancer patients and 14.6 months among neuroendocrine cancer patients. Overall survival came in at a median 9.4 and 24.0 months, respectively. Response rates in the overall study population were as follows:

- 9.2% for partial response
- 60.0% for stable disease
- 30.8% for progressive disease
- 0.0% for complete response

Five deaths occurred among study participants, but none were judged to be treatment related. Grade 4 adverse events included:

- Four cases of elevated bilirubin (liver enzyme)
- Five cases of liver dysfunction
- Four cases of infection
- Four cases of lymphopenia (diminished level of white blood cells)
- Four cases of pain
- Four cases of platelet abnormalities

Fatigue topped the list as the most common adverse event overall, at rates of 18% for grade 2 and 39% for grade 1. Though, investigators considered these "excellent tolerability and safety" results.

Benson A, et al., Safety, response and survival outcomes of 90Y radioembolization for liver metastases: Results from a 151 patient investigational device exemption multi-institutional study. SIR 2011, abstract 1.

12. **OncoDefender Can Assess Risk of Recurrence in Stage I/II Patients** (Mar.29/11)

The company Everist Genomics has announced the worldwide commercial availability of its OncoDefender-CRC colorectal cancer assay, the first and only molecular prognostic test capable of accurately predicting the risk of recurrence of cancer in patients previously treated with surgical resection of a **Stage I/II colon cancer tumor or Stage I rectal cancer tumor**. The OncoDefender-CRC test examines expression levels of a panel of genes extracted from cancer tissue taken at the time of surgery, and uses a proprietary computer-generated decision rule to identify patients who are at risk of recurrence. Patients identified by OncoDefender-CRC at high-risk of cancer recurrence may benefit from adjuvant therapy (post surgical chemotherapy) or other more aggressive treatment options. The prognostic test is capable of assessing recurrence risk in early stage colorectal cancer patients, **including the neglected stage I subset, where the lack of positive predictive prognostics presents a significant unmet need**. OncoDefender-CRC was developed through extensive clinical research and assay validation studies involving over 500 patients from around the world. OncoDefender-CRC will help physicians make patient management decisions that promptly and reliably direct the most effective treatment to those individual Stage I/II colon cancer and Stage I rectal cancer patients at high risk for tumor recurrence, while minimizing the exposure of low-risk patients to unnecessary, costly, and potentially toxic chemotherapy and/or radiotherapy. Traditional standards for assessing a patient's risk of cancer recurrence have depended solely on the cancer's anatomical characteristics (e.g. tumor size, depth of tissue invasion and migration to other organs and tissues). OncoDefender-CRC determines the tumor's aggressiveness based on its genetic makeup and molecular profile. The clinical data indicate that the performance characteristics of the OncoDefender-CRC test are superior to other methods currently in use to predict recurrence. Researchers maintain that knowing a patient's risk of recurrence after surgery directly informs decisions regarding post-operative treatment and the aggressiveness of follow-up. Molecular prognostics are valuable tools that reflect a tumor's underlying biology better than traditional examination and staging. The OncoDefender-CRC test is an important medical advance because it helps physicians identify aggressive tumors amongst stage I and II colorectal cancer patients. Physicians now have a valuable new prognostic tool to help them identify patients at risk of recurrence and most likely to benefit from adjuvant therapy.

<http://finance.yahoo.com/news/Everist-Genomics-Announces-prnews-1048814864.html?x=0&.v=2>

13. **Automated Reminder System for Colonoscopy Deemed Effective** (Mar. 30/11)

The simple practice of letters and a telephone call to patients who are due for a colonoscopy significantly improves adherence to endoscopic follow-up recommendations, according to the results of this new study. The results provide justification for the creation of reminder systems to improve colorectal cancer screening rates. The automated, patient-dependent colonoscopy follow-up reminder system significantly improved adherence with recommended surveillance colonoscopy and patient satisfaction. In this study, patients were assigned to groups that received the standard of care or a newly developed follow-up system that included a letter to the primary care provider, two letters to the patient and a telephone call to patients who had not yet scheduled an examination by the procedure due date. Doctors created and tested an electronic medical record-based system that reminds patients and providers when follow-up examinations - in this case, colonoscopies - are due and provides documentation in the medical record of this communication. The low-cost intervention almost doubled the rate of recommended exams during the time period of the study. Also, the intervention was well received by patients and even more effective in minority populations who typically receive lower quality care. This could lead to improvements in disparities in care for those needing repeat colonoscopies. Although evidence-based guidelines for colon cancer screening and surveillance exist, there are significant issues with patient adherence to recommendations regarding colonoscopy. In fact, colonoscopy presents particular difficulty for both patients and providers because of variability in the recommended follow-up interval and long length of time between examinations. After an initial colonoscopy is performed, appropriate follow-up testing often is neglected with potentially serious consequences. Few institutions or practices, however, have implemented systems to monitor and improve compliance with suggested follow-up tests. Regardless of whether information is transmitted on paper, in e-mails, texts or other media, investigators anticipate that the need for integrated systems to assist in prompting patients to obtain recommended care will increase. As electronic medical record systems are adopted and refined, protocols for notifying and documenting communication regarding recommended follow-up screening and diagnostic procedures should be strongly considered. Investigators concluded that although there are some upfront costs associated with the adoption of a follow-up system, once running, well-designed systems can function with little additional burden to the physician or administrative staff.

<http://www.sciencedaily.com/releases/2011/03/110329134258.htm>

14. **Utilization of Virtual Colonoscopy Triples in the U.S.** (Apr.6/11)

According to the results of this study, nationwide utilization of computed tomographic colonography (CTC), commonly referred to as virtual colonoscopy, has tripled in recent years. CTC employs virtual reality technology to produce a three-dimensional visualization that permits a thorough and minimally invasive evaluation of the entire colon and rectum. CT colonography is an alternative to conventional optical colonoscopy for colorectal cancer screening and diagnosis. Since most colon cancers develop from polyps, and screening to find and remove these polyps can prevent colon cancer, an opportunity exists to save lives with early detection. CTC, which is an American Cancer Society recommended

screening exam, can attract more people to be screened and save more lives through early detection of disease. Several well-designed multicenter trials now corroborate the results of an earlier landmark trial demonstrating equivalent performance of conventional optical colonoscopy and CTC in screening for cancer and precancerous polyps. The rapid expansion of the use of diagnostic CTC, even in the absence of Medicare coverage for screening CTC, speaks volumes to the need of an alternative exam for those who choose not to undergo colonoscopy. According to investigators, as more insurers provide coverage for CTC, access to CTC is likely to expand, increasing its utilization.

Duszak, Richard, et al., *Expanding Utilization and Regional Coverage of Diagnostic CT Colonography: Early Medicare Claims Experience*. *Journal of the American College of Radiology*, 2011; 8 (4): 235 DOI: [10.1016/j.jacr.2010.08.028](https://doi.org/10.1016/j.jacr.2010.08.028)

PSYCHOSOCIAL

15. Providing Quality of Life at End of Life Study (Mar. 30/11)

The Colorectal Cancer Association of Canada (CCAC) recently announced findings from the *Weighing Quality of Life in Cancer* National Survey showing that an alarming 82 per cent of Canadians have been touched closely by cancer and have had a close friend or family member battle cancer, or have done so themselves. The Survey also reveals concerns around quality of life and access to treatments in the late-stages of cancer, which tells us that we need to focus our efforts to meet the needs of patients with terminal, end-of-life cancers, particularly where we see high mortality rates, such as colorectal and lung cancer. Based on 2009 incidence rates, 40% of Canadian women and 45% of men will develop cancer during their lifetimes and an estimated one-in-four Canadians is expected to die from cancer. These rates and the Survey data together indicate a need for greater emphasis on providing comfort and quality of life for terminal cancer patients. Moreover, the *Weighing Quality of Life in Cancer* Survey demonstrates that Canadians want additional treatment options, even after a terminal cancer diagnosis. When asked what they would spend their time doing if they only had a few more weeks to live, in addition to spending more time with family and friends, 35% of respondents said they would spend that time seeking options that may prolong life and prevent the cancer from progressing. Canadians are not only concerned about their own health, they are also compassionate towards others in need. Quality of life wishes extend to all close friends and family members. Not surprisingly, almost all (87%) of Canadians feel that access to treatments that could prolong life for a few more weeks, with a good quality of life, would be valuable for their loved ones. This number remains high across all groups, even among those respondents without any close experiences with cancer in their lives. The *Weighing Quality of Life* Survey determined that part of maintaining quality of life is also providing greater access to therapies that treat metastatic cancers (late-stage cancer). However, results show regional disparities in the confidence levels of Canadians regarding access to these therapies. More than half of Canadians believe that where you live in Canada impacts your quality of treatment when diagnosed with cancer. In fact, only 4-in-10 Canadians indicate that they are very confident that their province is providing as much quality cancer treatment as other provinces in Canada. The Survey also shows that Canadians are concerned about provincial drug coverage, as 82% of Canadians believe that it is at least somewhat difficult to get access to the most current quality of life treatments from their province. When asked if Canadians would consider traveling outside their province for treatment, respondents indicated that they would prefer to seek cancer treatment in their home province. However, 7-in-10 Canadians indicated that they would travel out of province or country to seek treatment to extend their life by weeks or months. Providing access to quality treatments, especially during late stage cancer, should be a top priority for healthcare authorities across Canada. Comfort and quality of life are of utmost importance for patients and loved ones. It is important for medical professional and healthcare authorities to continue to weigh options for patients and make treatment decisions based on the personal needs and wishes of patients. Colorectal cancer has a significant impact on Canadians, affecting almost one-in-five or 17% of Survey participants. CCAC President, Barry Stein commented: "This is a burdensome type of cancer. It spreads quickly, and unfortunately we see many patients proceed to the metastatic or terminal stage. While there is no cure currently available, there are treatments that can improve quality of life for patients with terminal colorectal cancer – patients and caregivers should speak with their physician about the best available treatment options during the final weeks of life."

<http://smr.newswire.ca/en/ccac/cancer-hits-close-to-home-for-82-per-cent-of-canadians>

16. Stress of Cancer Makes it Difficult to Quit Smoking (Apr. 1/11)

Researchers at Wake Forest Baptist Medical Center recently conducted a study of 742 cancer patients and caregivers to determine why they can't throw the cigarettes away, and whether there are reasons beyond their addiction to nicotine. The study included patients with lung cancer, which is strongly associated with smoking, and colorectal cancer, which is not. What the researchers found is that having cancer "creates a very stressful period of time for everyone involved, and the added stress may make it a difficult time to quit". This includes caregivers, as well. For example, 18% of lung-cancer patients and 12% of colorectal-cancer patients continued to smoke after their diagnosis. Among caregivers, 25% continued to smoke, even though a family member had been diagnosed with lung cancer, as well as 20% of those whose family member had colorectal cancer. It is worrisome that such a number of cancer patients continue to smoke after a diagnosis. Smoking is a very addictive behavior, and it can be difficult to quit smoking. Many cancer patients do want to quit smoking and have tried many times in the past but have been unsuccessful. Investigators maintained that encouraging smokers to quit is important because other research shows that continuing could lead to development of new secondary cancers and

treatment complications, along with reduced overall survival rates and poorer quality of life. Investigators would like to ensure that cancer patients understand it is never too late to experience the health benefits of quitting smoking. How patients and caregivers respond after the diagnosis, including ending smoking, plays a key role in the treatment or in prolonging life. This is true even for stage 4 patients. Some with the more serious cancer diagnosis say it's futile to try to quit. They just want to enjoy the cigarettes and nicotine for the remainder of their life. That includes some patients smoking through a tracheotomy hole in their throat. For some caregivers, it can be a matter of denial that they choose not to quit themselves. Patients may say that their cancer was caused by some other factor, or it couldn't be cigarettes since they had a relative who smoked a pack a day as an adult and lived to be 92. Most caregivers try to encourage their loved one to quit, but some have more levels of influence than others. The study shows that physicians "need to be aware that a substantial number of their patients do continue to smoke after receiving a cancer diagnosis. They should be offered every encouragement and resource to quit."

<http://www2.journalnow.com/news/2011/mar/31/2/study-finds-stress-of-cancer-makes-it-harder-to-qu-ar-914238/>

OTHER

17. **No Link Between ABO Blood Group & Risk of Colorectal Cancer** (Mar. 11/11)

According to investigators, recent studies have shown an association between non-O blood group and risk of pancreatic cancer. It is unclear whether this association is observed with other gastrointestinal malignancies, including colorectal cancers. The current study sought to examine the relationship between ABO blood group and the risk of incident colorectal cancer. During 996,779 person-years of follow-up, researchers documented 1025 incident cases of colorectal cancers. The researchers found that in two large prospective groups, they did not observe a statistically significant association between ABO blood group and risk of colorectal cancer. They, therefore, concluded that these results do not support an association between ABO blood group and risk of colorectal cancer.

Chan, Andrew, et al., ABO Blood group and risk of colorectal cancer. Cancer, Epidemiology, Biomarkers & Prevention. Published online first March 17, 2011.

18. **Link Between Stem Cells and Colorectal Cancer** (Mar.18/11)

Scientists at the Institute for Research in Biomedicine found colorectal cancer cells trigger a set of genes similar to those found in intestinal stem cells. The researchers compared genes that are activated in stem cells and specialized cells from a healthy intestine with the genes that are activated in tumor cells taken from patients. Results showed patients with colon cancer have a set of genes activated that is very similar to the set activated in stem cells. The more activated genes they have in common, the more likely it is that the patient's cancer will spread and relapse, researchers concluded. The results add to the hypothesis that cancer organizes itself hierarchically, in such a way that only "tumor stem cells" are able to initiate and propagate the cancer. The researchers suggested patients with colorectal cancer should undergo genetic tests of their intestinal epithelium in order to predict a higher risk of relapse. Colorectal cancer cells trigger a set of genes similar to those found in intestinal stem cells. The results of the study offer new possibilities for diagnosing and treating the disease. Investigators maintain that there are cells within the tumour that regenerate the disease, but they still know very little about the biological reasons why. The results have uncovered a close relation between intestinal stem cells (non-specialized cells that generate all cells within the intestine) and colorectal cancer. The researchers compared genes that are activated in cells from a healthy intestine – both stem cells and specialized cells – with the genes that are activated in tumour cells taken from patients. What is it about stem cells that allows them to promote cancer? By definition, stem cells renew tissues, including in this case the intestinal epithelium, and can produce up to 5 grams of intestinal epithelial cells each day. Scientists believe that tumours may exploit the capacity of these cells to renew indefinitely in order to grow and spread. Furthermore, while the majority of cells have an average lifespan of days, as in the case of intestinal epithelial cells, or even months, stem cells survive for many years, increasing the probability that their DNA will accumulate damage and that they will turn cancerous. One of the biggest hurdles that oncologists face is a lack of tools to identify which patients have a higher risk of relapse. Discovering a close relation between intestinal stem cells and the propagation of cancer is a clear breakthrough in this respect. The hypothesis that colorectal cancer requires a specific type of cell to develop and thrive has also been demonstrated in other types of cancer. This finding opens the door for the development of treatments aimed at these new targets in the fight against cancer: tumour stem cells.

Merlos-Suarez, Anna, et al., The intestinal stem cell program predicts colorectal cancer relapse and identifies tumor stem cell niches. Cell Stem Cell (2011) [doi: 10.1016/j.stem.2011.02.020]

19. **CRC Groups Join Together to Offer Clinical Trial Matching in the U.S.** (Apr. 4/11)

Leading colorectal cancer advocacy organizations Colon Cancer Alliance and Fight Colorectal Cancer announced that they are teaming up on an initiative to encourage patients with colorectal cancer to take charge of their diagnosis and learn about clinical trials. The Colorectal Cancer Clinical Trial Call to Action campaign matches colorectal cancer patients with currently recruiting clinical trials based on their

individual medical situation. The easy-to-use resources, powered by EmergingMed, help patients discuss with their doctor clinical trials that may be appropriate for them. The personalized service is free, confidential, and available to patients, loved ones and healthcare professionals. It may be accessed by clicking on the following link: <http://www.emergingmed.com/partners/FCRC/> Patients who participate in clinical trials also help further colorectal cancer research. Today's clinical trial could be tomorrow's standard treatment. Unfortunately the process of finding an appropriate trial can be mind-boggling to patients, which is why Fight Colorectal Cancer is pleased to join with EmergingMed and the Colon Cancer Alliance on this vital program.

http://fightcolorectalcancer.org/c3_news/2011/04/crc_groups_join_together_to_offer_clinical_trial_matching

20. A New Formula Developed to Help Determine Disease Free Survival

(Apr. 4/11)

A simple formula that incorporates tumor area and percentage of positive lymph nodes helps predict 5-year disease-free survival in colorectal cancer, and may be used to guide treatment, according to the results of this new study. Although tumor size is not part of the widely used TNM (tumor, node, and metastasis) staging system, investigators hypothesized that it would be important in determining disease-free survival. To test that hypothesis, they used data from pathology reports to calculate the tumor area-to-node ratio (T:N) for 63 patients with stage III colorectal cancer (CRC) who underwent resection from January 2000 to June 2008.

- Specifically, **tumor area** is based on the two largest tumor measures multiplied together.
- The **percentage of positive nodes** is based on the number of nodes that are positive divided by the total number of nodes harvested, then multiplied by 100.
- The **T:N ratio** is based on the tumor area divided by the percentage of positive nodes.

In all, 35 patients remained disease free at 5 years and 28 developed metastatic disease at a mean of 16.4 months. The mean T:N ratio was significantly higher (2.76) in the disease-free group, compared with 0.50 in the metastatic group, meaning that a higher ratio is a better prognostic sign. From the values, the risk of distant metastasis can be calculated for a specific T:N ratio. For example, a patient with a T:N ratio of 1.22 would have a 25% risk of developing metastatic disease in 5 years, compared with a 50% risk for a patient with a T:N ratio of 0.77 and a 75% risk for a patient with a T:N ratio of 0.26. Dr. Poritz, the lead investigator in the study, also presented two hypothetical patients to illustrate how the formula could be used to influence clinical decision making. Patient A had a small tumor with an area of 1.52 and 2 of 17 positive nodes. This resulted in a T:N ratio of 0.25 and a 75% risk of developing metastatic disease in 5 years. Patient B had a large tumor with an area of 28.3 and also 2 of 17 positive nodes. The T:N ratio would be 2.4, and the patient would have only a 2% chance of developing metastatic disease within 5 years. "If you only looked at the number of nodes or [percentage of positive nodes], you might consider treating these patients in exactly the same manner, or at least consider their risk of developing metastatic cancer to be exactly the same, however, when you use our calculations, you can see that tumor volume is very important, and it changes the risk of developing metastatic disease dramatically in these patients. In this context, you might want to treat patient A more aggressively than patient B." Dr. Poritz also commented on the depth of penetration being less important than the size of the tumor: "the depth of penetration is included in the TNM staging system and it remains important, especially in stage II and node-negative disease when clinicians are trying to determine who should receive chemotherapy. However, the data would suggest that at least within stage III disease, tumor area may be more important than T stage, which has not been shown to correlate well with prognosis either in their study or others".

http://www.nxtbook.com/nxtbooks/elsevier/im_20110315/#/0

NUTRITION & HEALTHY LIFESTYLE

21. Gene Discovered to Be Linked to Colorectal Cancer When Folate is Low

(Mar.29/11)

The results of this new study provide evidence that a combination of folate deficiency and reduced expression of the **SHMT1 gene**, which is required for accurate DNA production, boosts the risk of colon cancer in mice. The study indicates that the SHMT1 gene may be a factor in itself, and also demonstrates how dietary folate, a B vitamin, may interact with an individual's genetic make-up to increase colon cancer risk. The same researchers implicated this gene as a cause of neural tube defects, a common class of birth defects. Nutrition and genetics work together to contribute to the creation of cancer cells, and based on the similarity of folate metabolism in mice and humans, it is likely that this gene is associated with human colon cancer. In the study, investigators found that the interactions among nutrients and genetic factors play an important role in the development of numerous cancers, including colorectal cancer. Molecular precursors that promote development of sporadic colon cancer include DNA damage. Lack of critical nutrients (such as folate) increases rates of DNA damage. Therefore, lack of folate has the potential to induce this damage that ultimately results in the progression of colon cancer. Screening for colorectal cancer is recommended to all individuals over age 50; however, close to 40 percent of the U.S. population in this age group does not take this precautionary method. Individuals who choose not to pursue colonoscopies may want to ensure that their diets contain adequate amounts of folate, according the lead investigator. The U.S. recommended daily allowance for folate is 400

micrograms per day. Foods that are rich in folate include many fruits and vegetables, grains, legumes, nuts and seeds.

Stover, Patrick J, et al., Shmt1 heterozygosity impairs folate-dependent thymidylate synthesis capacity and modifies risk of Apcmin-mediated intestinal cancer risk. Cancer Research. 71;6: p. 2098