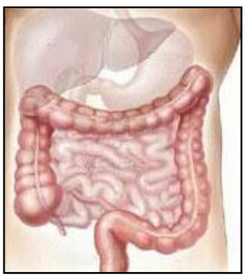
COLORECTAL CANCER RESEARCH

Month Ending June 24th , 2011



The following colorectal cancer research update extends from May 16th, 2011 – June 24th, 2011 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. **EGFR-Targeted Therapies Like Erbitux & Vectibix Bind to Decoy Receptor** (May 19/11)

Researchers at Yale School of Medicine have found that cancer drugs designed to target the epidermal growth factor receptor (EGFR), such as Erbitux and Vectibix, to inhibit cancer cell growth may not work because they also bind to a related receptor, serum sEGFR, with the same affinity. This may explain why these drugs were shown to be ineffective in two phase III clinical trials involving patients with colorectal cancer and suggests people get screened for **sEGFR** levels to determine if they will benefit from treatment with the drug. sEGFR concentrations vary widely in people with cancer and change in those taking the drug. Reagents designed to measure blood sEGFR also measure alpha-5 integrin, present on the surface of tumor cells which leads researchers to hypothesize that sEGFR plays a role in metastasis.

http://calorielab.com/labnotes/20110515/egfr-cancer-drugs-bind-segfr-decoy-receptor/

2. Biothera Initiates Dosing in a Phase III Trial in Colorectal Cancer Patients (May 19/11)

Biothera began dosing patients in a Phase III trial evaluating Imprime PGG® in combination with cetuximab (Erbitux®) as a potential new treatment for recurrent or progressive KRAS wild-type colorectal cancer. The trial design is built on data obtained in the company's previous clinical studies in colorectal cancer. Biothera has reviewed these results, as well as the protocol for the Phase III study, with the U.S. Food and Drug Administration. The endpoints for the study are designed to include an opportunity for accelerated approval based on interim data. Late stage colorectal cancer patients who can neither tolerate nor benefit from chemotherapy represent a large unmet clinical need. Based on previous trials, the company is confident that the combination of Imprime PGG and cetuximab will prove effective in treating this disease and further extending the survival and quality of life in these patients. The open-label, randomized study will enroll up to 795 patients and will be conducted in over 50 locations worldwide, including the U.S., Europe and South America. Patients will be randomized to one of two study arms in a 2:1 ratio. A total of 530 subjects in Arm 1 will receive Imprime PGG and cetuximab and a total of 265 subjects in Arm 2 will receive cetuximab alone. The patients must have received at least two prior chemotherapeutic regiments and cannot have been previously treated with cetuximab or panitumumab. The primary endpoint for the study is overall survival. Secondary endpoints are progression-free survival, tumor response and quality of life. Imprime PGG® is a novel immunomodulatory drug in development as a cancer therapy. Neutrophils are the most abundant immune cell in the body and normally responsible for pathogen killing, but not anti-tumor activity. In preclinical cancer models, however, Imprime PGG has been shown to bind to neutrophils and harness their killing ability to reduce tumor growth and enhance long-term survival. This targeted mechanism is synergistic with multiple anti-tumor monoclonal antibodies, demonstrating the potential to improve patient outcomes in a wide range of cancer indications.

http://www.businesswire.com/news/home/20110518006799/en/Biothera-Initiates-Dosing-Phase-III-Trial-Colorectal

3. DNA Repair Plays a Role in Colon Cancer Recurrence (May 24/11)

A new study shows a person's DNA repair system may play a role in determining if their cancer will recur. Investigators found colorectal cancer patients with defects in ***mismatched repair*** -- one of the body's systems for repairing DNA damage -- have *lower rates of recurrence* and better survival rates. About 15% of colorectal cancers are associated with mismatch repair defects. Researchers say it has never been clear whether these mismatches are linked to cancer recurrence rates, time-to-recurrence and site of recurrence. They also have been unclear about whether such defects affect responses to chemotherapy. Investigators from the Mayo Clinic in Rochester, Minn., analyzed data from more than 2,000 clinical trial patients who had been treated after surgery with chemotherapy that included 5-fluorouracil (5-FU) -- a standard drug used in colorectal cancer. The patients had either stage II or stage III colon cancer. Whether or not mismatched repair status influences response to 5-FU has been debatable. Results from this study, however, showed treatment with 5-FU reduced recurrence rates in stage III patients ***regardless of mismatch repair status but not stage II patients***. The investigators also compared the effects of 5-FU-based therapy in patients thought to have inherited mismatch repair defects versus those whose defects that occurred sporadically. They found 5-FU appeared to reduce recurrences only in those with inherited defects. Investigators concluded that the data demonstrate that patients with defective mismatch repair colon cancers have a statistically significant reduction in their rates of tumor recurrence, a delayed time to recurrence, and better survival rates.

Kilen, Brian, et al., DNA Repair system affects colon cancer recurrence and survival. J of National Cancer Institute. Advance Access: doi 10.1093.jnci/djr205

4. Primary Tumor Response to Preoperative Chemoradiation With or Without Oxaliplatin (May 25/11)

Seven hundred forty-seven patients with resectable, locally advanced (cT3-4 and/or cN1-2) adenocarcinoma of the mid-low rectum were randomly assigned to receive pelvic radiation and concomitant infused fluorouracil (5FU) either alone (arm A, n = 379) or combined with oxaliplatin (arm B, n = 368). Overall survival was the primary end point. Investigators concluded that adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy significantly increases toxicity **without** affecting primary tumor response. Longer follow-up is needed to assess the impact on efficacy end points.

Aschele, Carlo, et al., Primary Tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Onc. Published online before print. Doi: 10.1200/JCO.2010.34.4911

5. Avastin in First Line Therapy Comparing Folfiri and Xeliri (May 30/11)

The antivascular endothelial growth factor monoclonal antibody bevacizumab (better known as avastin) with infusional 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) is a standard first-line treatment option for metastatic colorectal cancer. However, clinical data for capecitabine and irinotecan (XELIRI) with bevacizumab are limited. A retrospective study was conducted on 139 patients with metastatic colorectal cancer to assess the efficacy and safety of first-line bevacizumab in combination with XELIRI **or** FOLFIRI. Primary endpoints were overall response rate (ORR), disease control rate and radical resection rate. Secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety. According to the investigators, no significant differences in efficacy were observed between patients administered XELIRI or FOLFIRI with bevacizumab. The ORR, median OS and PFS and recorded adverse events (AEs) were comparable to those previously reported, with no new or unexpected AEs observed. Investigators concluded that bevacizumab is similarly efficacious and well tolerated when administered with XELIRI or FOLFIRI.

Ocvirk, Janja, et al., Bevacizumab in first line therapy of metastatic colorectal cancer: a retrospective comparison of folfiri and xeliri. AntiCancer Research. Vol. 31, No. 5: pp. 1777-1782

6. Study Shows No Benefit from Adding Erbitux to Standard Chemo (Jun. 3/11)

According to the results of this study, the targeted therapy cetuximab (better known as erbitux) does not improve progression-free survival (PFS) or overall survival (OS) when added to standard chemotherapy as a first-line treatment for advanced colorectal cancer. The unexpected results of the COIN trial show that even patients without KRAS mutations in their tumour (the sub-group that showed a benefit from this therapy in other trials) did not benefit from the addition of cetuximab. And, in a second part of the COIN study, investigators commented that for the majority of patients with a normal platelet count before starting treatment, taking breaks from standard chemotherapy might improve quality of life (less time on chemotherapy, fewer hospital visits, and reduced side-effects) without compromising survival. The COIN study enrolled nearly 2500 previously untreated patients with advanced colorectal cancer from 111 hospitals across the UK and Ireland to investigate whether the addition of a monoclonal antibody (cetuximab) to standard chemotherapy might improve survival, and to establish whether taking treatment holidays from standard chemotherapy might improve quality of life without compromising survival. Patients were randomly assigned to a continuous combination of oxaliplatin and fluoropyrimidine, the same continuous combination plus cetuximab, or the same combination chemotherapy in an intermittent schedule. Apart from a modest increase in the rate of tumour shrinkage, cetuximab had no significant benefit on PFS or OS. Interestingly, even patients with a KRAS wild-type (normal) gene in their tumour (who in theory should have benefited from the addition of cetuximab) did not differ in their OS or PFS. The authors say: "*The use of cetuximab in combination with oxaliplatin and capecitabine in first-line chemotherapy in patients with widespread metastases cannot be recommended. However, the trial showed the powerful effect of the presence of specific mutations in the tumour on prognosis and this should influence future clinical trials in bowel cancer."* The COIN trial also assessed whether it might be possible to shorten the duration of initial chemotherapy to 12 weeks and then restart on disease progression by comparing standard continuous chemotherapy with the same chemotherapy given with planned treatment holidays (intermittent chemotherapy). Findings showed that intermittent chemotherapy did not increase or significantly decrease survival. However, platelet count before starting intermittent chemotherapy was identified as a potentially valuable predictor of survival and quality of life. A raised platelet count resulted in a 5-month reduction in survival and impaired quality of life, whereas for the three-quarters of patients with normal platelet counts, time off chemotherapy was associated with improved quality of life (less time on chemotherapy, fewer hospital visits, and reduced neuropathy and hand-foot syndrome [redness, swelling, tenderness, and peeling of palms and soles]) with similar survival. The authors remark: "There seems to be a large subpopulation of patients for whom intermittent therapy provides similar survival benefit and the results of this trial provide a basis for discussion of options between patients and clinicians."

http://www.medicalnewstoday.com/releases/227421.php

7. VEGF-C and VEGF-D Identified as Biomarkers for Avastin Resistance (Jun.4/11)

Circadian Technologies Limited (ASX: CIR) announced the presentation of data at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago associating resistance to Avastin® with increases in plasma VEGF-C and D concentrations. Resistance to Avastin® is a frequent occurrence in the treatment of certain cancers such as colorectal cancer with resulting loss of response and disease progression. The study, which was led by Drs Lieu and Kopetz at The University of Texas MD Anderson Cancer Center showed that increases in VEGF-family markers in patients with metastatic colorectal cancer are associated with Avastin® resistance. In particular, VEGF-C increases were seen in patients prior to and at the time of disease progression while receiving Avastin® and chemotherapy. The data show that the VEGF-family ligands, other than VEGF itself, are associated with Avastin®-containing

chemotherapy resistance in patients with metastatic colorectal cancer and investigators are planning prospective confirmatory studies to further evaluate and validate these findings.

http://www.reuters.com/article/2011/06/06/idUS196530+06-Jun-2011+PRN20110606

8. Breast Cancer Drug Lapatinib Helpful in Colon Cancer (Jun. 4/11)

A new treatment for colon cancer that combines a chemotherapy agent approved to treat breast cancer and a cancer-fighting antibody is now ready to proceed to clinical trials. Researchers tested ***lapatinib***, a targeted chemotherapy agent currently approved for breast cancer treatment, in a new combination with artificial antibodies that mimic a natural cancer-fighting protein produced in the human body. The monoclonal antibodies **mapatumumab** and **lexatumumab** act similarly to TRAIL -- tumor necrosis factor [TNF]-related apoptosis-inducing ligand -- a naturally occurring molecule in the body that tells a cell it is time to die. TRAIL sets a process in motion that targets and shuts down tumor cells and keeps them from spreading. The TRAIL receptors -- death receptors -- on the cancer cells respond to TRAIL by dying. The artificial antibodies act as surrogates of TRAIL by activating the same signaling pathway resulting in tumor cell death. The monoclonal antibodies have an advantage over TRAIL because they remain active in the body for a longer period of time. TRAIL receptor antibodies last for less than 30 minutes, while the artificial monoclonal antibodies last for about 9 days. Although the antibodies can act similarly to TRAIL, they do not completely substitute for TRAIL and ultimately which one gets used in what situation is still being tested in clinical trials. But for the purpose of these new advances, either one works. Lapatinib (also known as Tykerb) increases the amount of "death receptor" protein available for TRAIL to do its job -- killing off cancerous cells. The researchers tested the lapatinib and monoclonal antibody combination in mice. Separately, the two treatments did not increase tumor cell suppression -- but when the drugs were administered together, the researcher found that cell death escalated.

El-Deiry, Wafik S., et al., Off-Target Lapatinib Activity Sensitizes Colon Cancer Cells Through TRAIL Death Receptor Up-Regulation. **Science Translational Medicine*, 2011; 3 (86): 86ra50 DOI: 10.1126/scitranslmed.3001384***

9. Xeloxgem (Xeloda + Oxaliplatin + Gemcitabine) In Second Line Therapy (Jun. 4/11)

Capecitabine plus oxaliplatin (XELOX) is an effective second-line regimen for advanced colorectal cancer (CRC) patients pretreated with irinotecan. Previous studies have shown supra-additive anti-tumor activity of gemcitabine (GEM) when administered with oxaliplatin. Researchers investigated the dose, toxicity, and efficacy of a second-line XELOXGEM regimen in CRC patients pretreated with irinotecan. Patients with metastatic or recurrent CRC who failed after a first-line irinotecan-containing regimen received escalating doses of gemcitabine followed by capecitabine and oxaliplatin on a 21-day cycle. Ten (26.3%) and 23 (60.5%) patients experienced partial response and stable disease, respectively. The median progression-free survival and overall survival were 5.4 months and 17.7 months respectively. Researchers concluded that the XELOXGEM triplet combination is an active and safe second-line regimen for advanced CRC patients pretreated with irinotecan.

Kim, Se Hyun, et al., Combining capecitabine, oxaliplatin, and gemcitabine (xeloxgem) for colorectal carcinoma patients pretreated with irinotecan: a multicenter phase I/II trial. Cancer Chemotherapy and Pharmacology. Doi: 10.1007/s00280-011-1668-y

10. Adding Oxaliplatin to 5FU/Leucovorin in Stage II Colon Cancer (Jun. 6/11)

Ins this study, researchers investigated the addition of Oxaliplatin to 5FU/Leucovorin in patients with stage II colon cancer. The analysis includes 4,883 patients with stage II and III colon cancer (2009 with stage II disease) treated using 5FU/Leucovorin regimens, and 3,788 patients with stage II and III colon cancer (991 with stage II disease) treated with FU/L + Oxaliplatin. Patients from 4 NSABP trials were included. Only in one of the trials (C-07) was there random assignment to Oxaliplatin. Overall, there was a highly significant benefit of Oxaliplatin for DFS (disease free survival) and OS (overall survival) in patients with stage II and III disease combined. According to the researchers, the effect of Oxaliplatin remained significant for DFS and OS in stage III. For stage II, Oxaliplatin did not significantly improve outcomes.

Yothers, GA, et al., The efficacy of oxaliplatin when added to 5Fluorouracil/leucovorin (FU/L) in stage II colon cancer. ASCO 2011: Abstract 3507. J Clin Oncol 29: 2011

11. Erbitux + Folfiri As First Line Therapy for MCRC (Jun. 6/11)

Cetuximab (better known as erbitux) is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR). In phase III studies, cetuximab has been shown to improve outcomes when added to standard chemotherapy for treatment of metastatic colorectal cancer. The Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study showed reductions in risk of progression and tumor response in patients who received cetuximab in addition to a chemotherapy regimen of irinotecan, infusional fluorouracil, and leucovorin (FOLFIRI). In particular, the benefits of cetuximab appeared to be ***limited to patients whose tumors were wild-type at the KRAS gene***. This study is an updated analysis of the CRYSTAL study that evaluates outcomes after a longer follow-up time

and in a larger number of patients evaluated for KRAS status. In addition, the significance of the BRAF gene, which is a downstream effector of KRAS was evaluated. This was a retrospective subgroup analysis of KRAS mutation status in patients enrolled in an open-label, randomized, multicenter, phase III study of cetuximab plus FOLFIRI **or** FOLFIRI alone as first-line treatment for metastatic colorectal cancer. Among patients whose tumors were wild-type for KRAS, cetuximab plus FOLFIRI resulted in **significantly reduced risk of disease progression** (median progression free survival [PFS], 9.9 vs 8.4 months;), **significantly improved overall survival** (23.5 vs 20.0 months;), and significantly increased odds of response (best overall response rate 57.3% vs 39.7%;) compared with FOLFIRI alone. Among patients with wild-type KRAS, those in the cetuximab plus FOLFIRI group who developed early acne-like rash had significantly prolonged survival time compared with those who did not develop early acne-like rash (26.4 vs 19.1 months). ***Among patients with mutations in KRAS, the addition of cetuximab did not improve PFS, overall survival, or best overall response***. KRAS mutations were associated with worse overall survival in both treatment groups compared with wild-type. Treatment effect and KRAS mutation status were associated with significant interaction effects for PFS, overall survival, and best overall response. A total of 60 of 999 (6%) tumor samples evaluated for both BRAF and KRAS had BRAF V600E mutations. All but 1 patient with BRAF were wild-type for KRAS. ***Patients who were wild-type for both genes who received cetuximab plus FOLFIRI had significantly reduced risk of disease progression and significantly increased odds of response compared with FOLFIRI alone, but overall survival no longer differed significantly between treatment groups***. BRAF mutation status was not associated with a significant treatment interaction effect, but was associated with worse outcomes in both treatment groups. KRAS mutation status was not associated with differences in safety outcomes.

Van Cutsem, E, et al., Cetuximab plus irinotecan, fluorouracil, and leucovorin as first line treatment for metastatic colorectal cnacer: updated analysis of overall survival according to tumor kras and braf mutation status. J Clin Oncol. 2011. Epub Ahead of print.

SURGICAL THERAPIES

12. MSI Testing Before Surgery For Young Patients (May 19/11)

Lynch patients are at high risk for a second or third colon cancer, so identifying them ***before*** their colorectal surgery may change the operation planned. Surgeons may want to remove the entire colon to prevent another colon cancer, and women may choose to have a hysterectomy during the same surgery to prevent endometrial cancer. Because young patients are more likely to have Lynch syndrome, pathologists at the Mayo Clinic tested tumors from patients 50 years old or younger for microsatellite instability (MSI) after their surgery if they had not been tested preoperatively. Comparing those with preoperative MSI testing to those whose tumors were tested after surgery gave the pathology team a chance to see if preoperative testing changed the surgical plan. Between 2003 and 2008, 210 young patients with colorectal cancer had MSI testing, either before or after their surgery"

- 13% had high microsatellite instability (MSI-H).
- Two out of three (63%) of MSI-H patients had an inherited Lynch syndrome mutation.

Doctors knew before surgery that 16 patients had MSI-H tumors, but they only knew for sure that 2 of the 16 had Lynch syndrome because of genetic testing. For the 16:

- 7 (43.8%) had at least one first-degree relative with colorectal cancer
- 13 (81.3%) had any family history of colorectal cancer
- Surgeons recommended that a complete colectomy be done at the time of their surgery for 15 of the 16.
- 11 of 16 had colectomy performed.
- 8 out of the 10 women had a hysterectomy.
- 12 of 16 had genetic testing for Lynch syndrome done, 2 prior to surgery.
- 9 of 16 (56.3%) tested positive for Lynch.

There were 12 patients who weren't tested before surgery but tested MSI-H postoperatively. For that group:

- 2 (16.7%) had a first degree relative with colorectal cancer
- 5 (41.7%) had any family history of colorectal cancer
- 1 had colectomy recommended prior to surgery and that individual did have the colon removed.

- The 1 female did not have a hysterectomy.
- 4 out of the 12 had a genetic blood test for Lynch syndrome.
- 1 was positive.

Investigators concluded: “MSI-H status was found in 13% of young-onset colorectal cancer patients operated at our institution, and 63% of those tested, had germ-line mutations. Knowledge of MSI status preoperatively significantly influenced surgical management with an increase in total colectomy and hysterectomy compared to patients whose MSI-H status was discovered postoperatively. The absence of germ-line testing in MSI-H patients did not appear to influence surgical decision making.”

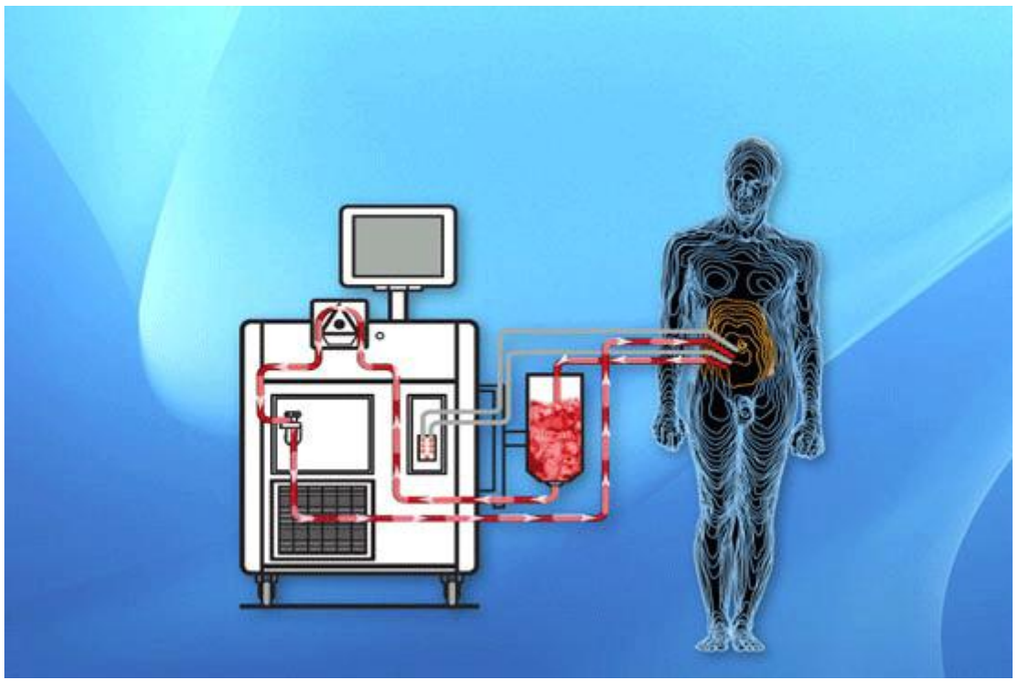
Holder-Murray, Digestive Disease Week 2011, poster Session, Mo 1599, Impact of Preoperative Microsatellite Instability Testing On Surgical Management in Young Onset Colorectal Cancer Patients: Results from a Reflex Testing Protocol.

13. Second Surgery for Peritoneal Mets (May 19/11)

Some colorectal cancer patients will have their cancer spread into the tissue within their abdomen or to the surfaces of abdominal organs. This condition, called ***peritoneal carcinomatosis (PC)***, can be treated successfully if it is recognized early. Unfortunately, it is often not seen on routine scanning and not diagnosed when surgical treatment is possible. A clinical trial at the NIH Clinical Center in Bethesda will see if a second surgery to look for peritoneal carcinomatosis in high-risk patients can find the disease earlier, treat it appropriately, and improve survival. Eligible patients for the trial will have already had surgery that removed all visible tumors and are considered to have *no evidence of disease (NED).* However, their cancer will have some high-risk features that makes it more likely for them to develop peritoneal carcinomatosis in the future. The trial is not intended for patients who already have peritoneal carcinomatosis. Between 11 and 14 months after their original surgery patients at high-risk for peritoneal cancer recurrence but with no current evidence of disease will be randomly assigned to have their follow-up care provided by:

- Standard-of-care surveillance with blood tests, physical exams, and CT scanning, **or**
- Mandatory second-look surgery (MSLS).

If peritoneal carcinomatosis is found on second-look surgery, all visible tumor will be removed (*cytoreduction)* and heated intraperitoneal chemotherapy (HIPEC) infused into the abdomen at the end of surgery.



During the HIPEC procedure, the surgeon will continuously circulate a heated sterile solution--containing a chemotherapeutic agent--throughout the peritoneal cavity, for a maximum of two hours. The HIPEC procedure is designed to attempt to kill any remaining cancer cells. The procedure also improves drug absorption and effect with minimal exposure to the rest of the body. In this way, the normal side effects of chemotherapy can be avoided. Source: http://www.hipectreatment.com/documents/hipec.php

High-risk features that increase risk for PC and make patients eligible for the trial include colorectal cancer that:

- Perforated into the peritoneal cavity.
- Included minimal peritoneal carcinomatosis (PC) which was completely surgically removed at the time of initial operation.

- Was a T4 lesion that required surgery to remove additional organs along with the colon or rectal tumor.
- Was associated with ovarian metastases.
- Presented as an emergency with tumors associated with obstruction and/or bleeding.

Patients who had limited extra abdominal metastases at the time of diagnosis may be eligible if the lesions were completely removed surgically and the patient remains NED. **More information about the trial is available from the principal investigator:**

- Itzhak Avital, M.D. Principal Investigator
- Phone: 301-402-0083 301-402-0083
- Fax: 301-496-0734
- Email: avitali@mail.nih.gov

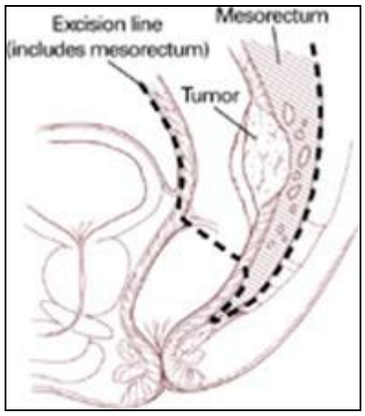
To enroll in the trial or make a referral:

- Melissa Walker, R.N., B.S.N. Research Nurse
- Phone: 301-451-6940
- Fax: 301-594-5356
- Email: walkerme@mail.nih.gov

http://fightcolorectalcancer.org/uncategorized/2011/05/second_look_surgery_for_peritoneal_carcinomatosis

14. Preoperative Radiotherapy Combined with Total Mesorectal Excision For Rectal Cancer (May19/11)

The TME trial investigated the value of preoperative short-term radiotherapy in combination with total mesorectal excision (TME).



In TME, the rectum and the mesorectum are removed. The mesorectum is the area of fatty tissue below the rectum that contains lymph nodes, which are the most common area for the cancer to spread.

Source: *http://www.colorectal-ancer.ca/extras/physician/common/print/21.html*

1861 patients with resectable rectal cancer without evidence of distant disease were randomly assigned to TME preceded by 5 × 5 Gy radiotherapy or TME alone (ratio 1:1). The primary endpoint to be measured was local recurrence, analyzed for all eligible patients who underwent a complete local resection. For all eligible patients, preoperative short-term radiotherapy reduced 10-year local recurrence by more than 50% relative to surgery alone without an overall survival benefit. For patients with a negative resection margin, the effect of radiotherapy was irrespective of the distance from the anal verge and led to an improved cancer-specific survival. Nevertheless, preoperative short-term radiotherapy significantly improved 10-year survival in patients with a negative circumferential margin and TNM stage III.

Van Gijn, Willem, et al., Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12 year follow up of the multicentre, randomized controlled TME Trial. The Lancet Oncology, Vol. 12, Issue 6, pp. 575-582

15. Prognosis of Elderly Colorectal Cancer Patients In the Year Following Surgery (May. 24/11)

According to some of the literature, elderly colorectal cancer patients have worse prognosis than younger patients. Age-related survival differences may be cancer or treatment related, but also due to death from

other causes. This study aimed to compare population-based survival data for young (<65 years), aged (65–74 years), and elderly (≥75 years) colorectal cancer patients. All patients operated for stage I–III colorectal cancer between 1991 and 2005 in the western region of The Netherlands were included. A total of 9,397 stage I–III colorectal cancer patients were included in this study. According to the results, elderly colorectal cancer patients who survived the first year had the same cancer-related survival as younger patients. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Treatment of elderly colorectal cancer patients should focus on perioperative care and the first postoperative year.

Dekker, JWT, et al., Important of the first postoperative year in the prognosis of elderly colorectal cancer patients. Ann Surg Oncol. 2011 May 1. Vol. 18, Issue 6: pp. 1533-1539.

RADIATION / INTERVENTIONAL RADIOLOGY

16. The Use of Intraoperative Radiotherapy in Colorectal Cancer (May 20/11)

Intraoperative radiotherapy (IORT) has been proposed as an encouraging treatment for colorectal cancer. The aim of this study was to assess the efficacy and safety of IORT for colorectal cancer through a systematic review. Studies located in electronic databases were selected according to established criteria, read and analyzed and the results extracted by two independent reviewers. Fifteen studies met the selection criteria. Five-to-six-year local control (LC) was over 80% and 5-year overall survival (OS) was close to 65%. For recurrences, the 5-year overall survival was 30%. The main acute complications were gastrointestinal. According to the investigators, adding IORT to conventional treatment reduces the incidence of local recurrences within the radiation area over 10%. IORT is a safe technique as it does not increase toxicity associated with conventional treatment.

Cantero-Munoz, P,et al., Efficacy and safety of intraoperative radiotherapy in colorectal cancer: a systematic review. Cancer Lett. 2011 July 28; 306 (2): pp. 121-133

17. Pretargeted Radio-immunotherapy for Colorectal Cancer (Jun. 4/11)

In this study, investigators present results from a phase 1 clinical trial for a cancer therapy that has the potential to kill colorectal tumors with less destruction of healthy tissue. Further research could lead to the use of this ***radioimmunotherapy*** to eliminate residual cancer after surgery or as a standard treatment to keep tumors from returning or spreading to other organs. Compared to the conventional way of guiding radiation to tumors with radiolabeled antibody, pretargeted radio-immunotherapy offers an attractive potential alternative because the delivery of therapeutic isotope is rapid and is separated from the long antibody delivery process, thereby reducing the harmful effects of radiation to the body, especially the bone marrow. In recent years the development of radioimmunotherapy has led to increasingly targeted cancer therapies that combine antibodies pinpointing specific physiological processes of the cancer and medical isotopes that deliver a dose of radiation to the cancer tissue. Pretargeted radioimmunotherapy takes this a step further by breaking the therapy into two phases. In the first phase, an antibody is infused that recognizes both an antigen from the tumor and the building blocks of proteins that serve as a vehicle for the radioisotope. When the antibody has cleared the rest of the patient's system, leaving only the tumor-bound antibody, a second phase is administered in the form of an injected small protein labeled with the medical isotope. The drug binds with the already tumor-bound antibody and delivers the radiation dose. The fraction of the drug that is not bound is quickly cleared from the rest of the body by the kidneys and out through the urine. The objective of this study -- the first of its kind to treat patients with metastatic, or spreading, colorectal cancer with pretargeted radioimmunotherapy -- was to improve patients' prognosis without compromising their quality of life. It is conducted in collaboration with Garden State Cancer Center, Belleville, Immunomedics Inc. and IBC Pharmaceuticals Inc. of Morris Plains, N.J., developers of the pretargeting mechanism and reagents. First, patients were administered a test-cycle to map the path and predict the radiation dose of the subsequent therapy injection. The antibody, TF2, was infused followed by the small protein, IMP288, carrying a non-therapeutic isotope, 111In, which was measured by whole-body planar and single photon emission computed tomography imaging. Patients were then administered TF2 again, and the therapeutic isotope and agent 177Lu-IMP288. Research showed effective targeting of tumors and minimal healthy tissue damage, which could lead the way for further studies with higher or multiple dosing strategies and greater targeting of cancer tissue.

Schoffelen, O., et al., Phase I clinical study of the feasibility of pretargeted radioimmunotherapy (PT-RAIT) in patients with colorectal cancer (crc): first results. SNM's 58th Annual Meeting, June 4-8, 2011. San Antonio, TX. Scientific paper 358.

SCREENING

18. Detecting Polyps in Women (May19/11)

Although many studies show that men have more adenomas (pre-cancerous polyps) than women, there is no difference in the rates of colorectal cancer between men and women. Could this be because women have polyps that are harder to detect during screening and so aren't removed in time to prevent

cancer? This question was addressed in the current study. In 600 consecutive colonoscopies, researchers counted the number of polyps overall, as well as those that were flat and those that were both flat and found in the upper part of the colon (*proximal)* since both flat and proximal polyps are harder to find. They used a high definition colonoscope to uncover even the most difficult polyps. They did find more polyps in men — 79 in the 248 men in the study. There were 71 in 352 women.

- But the women were much more likely to have flat adenomas: 41 of 71 or 57.7%.
- Men had 29/79 flat polyps or 39.7%.

In addition,

- Almost half (46.5%) of women's polyps were ***both*** flat and located in the proximal colon.
- For men, about 1 in 4 polyps (25.3%) were difficult to detect (flat, proximal adenomas).

Women were almost four times as likely to have a more serious advanced flat, proximal adenoma as men. Overall, 19.1% of the advanced male polyps were flat and proximal compared to 48% of the female ones.

Anderson, Joseph, et al., Digestive Disease Week 2011, Poster Su1538, Larger proportion of significant adenomas present as flat and proximal in women as compared to men: a prospective screening study using a high definition colonoscope.

19. People with Negative FOBT Might Still Be At Risk for Colorectal Cancer (May 19/11)

Individuals with a negative fecal test result at first screen (blood concentrations of less than 100 ng per mL) might be at increased risk of developing colorectal cancer in line with increasing fecal hemoglobin concentration. The findings suggest that initial fecal hemoglobin concentration could be used to define groups at low, intermediate, and high risk of developing new colorectal neoplasia (abnormal growth of cells), and might encourage some people who avoid repeat screening to be tested. Immunochemical fecal occult blood testing (iFOBT), which uses antibodies to detect hidden human blood (hemoglobin) in stool, is widely used to screen for colorectal cancer. It is well known that people with fecal haemoglobin concentrations higher than 100 ng per mL are at increased risk of colorectal neoplasia. However, little is known about the subsequent risk of developing colorectal cancer for people who have a negative result (ie, <100 ng per mL) at the first screen. In this study, a team from Taiwan led by Hsiu-Hsi Chen from the National Taiwan University, Taipei, Taiwan, examined the association between fecal hemoglobin concentration and risk of subsequent adenoma and colorectal cancers in individuals with negative findings at the first screen. They also calculated the subsequent risk for non-referrals (individuals with fecal hemoglobin concentrations higher than 100 ng/mL who refused colonoscopy) and false-positives (in whom colonoscopy did not find disease). Between 2001 and 2007, 44 324 participants from the Keelung community-based iFOBT screening program for residents aged 40-69 years with negative results at the first screen were followed up to find cases of colorectal neoplasia. Among individuals with negative results, hemoglobin concentration was predictive of neoplasia and subsequent progression to cancer. The higher the initial fecal hemoglobin concentration, the greater the likelihood of developing colorectal neoplasia. Non-referrals had the highest risk of colorectal neoplasia and false-positive cases the lowest risk. The authors suggest that fecal hemoglobin could be used to define groups at low, intermediate, and high risk and tailor screening strategies accordingly. They say: "Providing such risk stratification for participants with a negative finding at the first screen could enhance awareness among those with higher initial fecal hemoglobin concentration, particularly concentrations just under the usual threshold taken to indicate colorectal neoplasia." They conclude: "The findings not only confirm the value of using baseline fecal hemoglobin concentration as a measure of subsequent risk of colorectal cancer, but also show that rising fecal hemoglobin concentration is a sign of rising risk of colorectal cancer."

Chen, Li-Sheng, et al., Baseline faecaloccult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. The Lancet Oncology. Vol. 12, Issue 6: pp. 551-558

20. Oncotype DX Identifies Those Stage II Patients Who Are At Higher Risk of Recurrence (Jun. 13/11)

Gene expression profiling explores the patterns of genes' important information about prognosis or likely response to treatment in several types of cancer. For example, among women with early-stage, estrogen receptor-positive breast cancer, the Onco*type* DX® breast cancer test has been shown to predict the likelihood of cancer recurrence and the likelihood of benefit from chemotherapy. As a result, the test has been added to medical guidelines for early-stage breast cancer. A similar test may provide important information for patients with ***Stage II colon cancer***. Stage II colon cancer refers to cancer that extends through the wall of the colon but has not invaded lymph nodes or spread to distant parts of the body. Many patients with this stage of disease have good outcomes with surgery alone, and routine adjuvant (post-surgery) chemotherapy is not currently recommended for Stage II colon cancer. Chemotherapy may, however, be considered for Stage II patients with a higher risk of cancer recurrence. In the current study, the Onco*type* DX Recurrence Score and other factors were evaluated among patients with Stage II colon cancer who participated in the CALGB 9581 study.

- Even after accounting for factors such as stage, grade, number of lymph nodes examined, and mismatch repair (MMR) protein status, the Recurrence Score was a significant predictor of recurrence risk.
- The researchers also evaluated the Recurrence Score in a subset of patients for whom traditional factors such as grade do not provide prognostic information (patients with T3 stage II cancer and intact MMR protein function). Once again, the Recurrence Score was able to identify patients who had a high risk of cancer recurrence: five-year risk of recurrence was more than 20% among patients with the highest Recurrence Scores.

According to the investigators, these results confirm that the Onco*type* DX colon cancer test provides new information about recurrence risk in patients with Stage II colon cancer. The test may help guide treatment decisions by identifying patients with more aggressive disease.

Venook AP, et al. Validation of a 12-gene colon cancer recurrence score (RS) in patients (pts) with stage II colon cancer (CC) from CALGB 9581. Paper presented at: 2011 Annual Meeting of the American Society of Clinical Oncology; June 3-7, 2011; Chicago, IL. Abstract 3518.

21. Poor Bowel Preps May Miss Polyps (Jun. 6/11)

When bowel preps are not good, doctors may miss almost half of adenomas (polyps) during colonoscopy. Worse, they may miss nearly 1 in 3 large adenomas, the most worrisome kind. The bad news is that bowel prep may be suboptimal in as many of one in four patients. Because of the danger of missing an adenoma after poor bowel prep, some doctors will repeat the colonoscopy, particularly if they found at least one adenoma during the first exam. Doctors at Columbia University Medical Center reviewed all colonoscopies performed there from 2006 to 2008, as well as colonoscopies that were repeated within three years. Of nearly 13,000 colonoscopies, over 3,000 had suboptimal preparation, either fair or poor. Five hundred of those were repeated during the three year follow-up. In the 216 with good preparation for the second exam, 196 adenomas were found in all, 83 only on the second test, an adenoma miss rate of 42%. The miss rate for advanced adenomas was 27%. For colonoscopies that were repeated within a year, the miss rate for all adenomas was 35% and for advanced adenomas 35%. Although only a fraction of patients with poor preps had their exams repeated, the additional polyps which were probably missed on the first test were a serious problem. The lead investigator concluded: "Our findings of a miss rate of 42% for all adenomas and 27% for advanced adenomas suggest that suboptimal bowel preparation has a substantial harmful impact on the effectiveness of colonoscopy, and follow-up examination within one year should be considered. Because neoplastic findings on the initial colonoscopy were associated with a greater miss rate, a repeat examination within one year is indicated when an adenoma is found during a colonoscopy with suboptimal bowel preparation."

Lebwohl, Benjamin, et al., The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. Gastrointestinal Endoscopy. Vol. 73, Issue 6: pp. 1207-1214

OTHER

22. Trial Participation Possible for Elderly Patients (May 19/11)

According to the results of this study, elderly and frail patients with colorectal cancer can participate in randomized controlled trials with appropriate design, including reduced drug dosing. In the FOCUS2 study researchers randomized 459 frail and elderly patients with advanced colorectal cancer to 48-h intravenous fluorouracil with levofolinate; oxaliplatin and fluorouracil; capecitabine; or oxaliplatin and capecitabine. The investigators started treatment at 80% of standard doses, but could increase to full standard doses after six weeks if treatment was well tolerated. Although the primary end point of progression-free survival (PFS) was not met, the investigators found that patients most likely to benefit from chemotherapy were more active, had less widespread cancer, and had fewer symptoms. The investigators also found that oxaliplatin produced less benefit in frail and elderly patients than in younger and fitter patients; however, the drug significantly improved overall treatment utility, a measure of cancer shrinkage and survival time as well as patients' own assessment of treatment effectiveness and quality of life. The researchers also found that the use of oral chemotherapy as opposed to intravenous infusion resulted in more side effects and did not have any clear benefits. "With use of reduced starting drug doses, adapted for this population, combination chemotherapy including oxaliplatin seems, on balance, preferable to single-agent fluoropyrimidines, although the primary end point of PFS was not met. We did not, however, detect any advantage of capecitabine compared with fluorouracil," the authors write.

Seymour, Matthew, et al., Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (mrc focus2): an open-label, randomized factorial trial. The Lancet. Vol. 377, Issue 9779: pp. 1749-1759

NUTRITION & HEALTHY LIFESTYLE

23. Red and Processed Meat, Fibre and Colorectal Cancer (May 24/11)

This comprehensive and authoritative report, part of the World Cancer Research Fund (WCRF)/American Institute for Cancer Research's (AICR) Continuous Update Project, examined the impact of diet, physical activity and body weight on colorectal cancer risk. 10 new cohort studies on red and processed meats

were added to the existing 14 in the 2007 report and researchers concluded that there is compelling evidence linking red and processed meat consumption to a higher colorectal cancer risk. According to AICR, we should limit our red meat consumption to 18 ounces per week and should avoid all processed meats. After reviewing new evidence since the 2007 report, researchers also concluded that fiber protects much more against colorectal cancer than previously thought. While the 2007 report described fiber's protective qualities as probable, today these protective qualities are considered convincing. The AICR has estimated that about 45% of colorectal cancer cases could be prevented if we all,

- Ate more fibre-rich plant foods
- Ate less red meat
- Drank less alcohol
- Moved more and stayed lean

Colorectal Cancer Risk Higher If You Eat Red And Processed Meat, Lower If You Eat Fiber, http://anpron.eu/?p=5742

24. Reducing Exposure to Carcinogens When Cooking Outdoors (May 30/11)

There is evidence that frequently eating grilled meats can increase the risk of certain types of cancer, including colorectal cancer. When meats are grilled, broiled, or seared, the high cooking temperature breaks down the amino acid creatine (an amino acid found in muscle), forming chemicals called heterocyclic amines (HCAs). The federal government added HCAs to its list of known carcinogens in 2005. Since HCAs are mutagens, they can bind directly to DNA, causing the kind of mutation that can promote formation of cancerous cells. Studies have linked frequent ingestion of HCAs to an increased risk of pancreatic and colorectal cancers. According to a Cancer Project study, sponsored by the Physicians Committee for Responsible Medicine, the top five grilled meats recorded with the highest concentrations of HCAs (in order of highest concentration to lowest) are chicken breast, steak, pork, salmon and hamburger. Meat lovers, however, do not need to give up grilling meat altogether in order to reduce their risk of cancer. Instead, the following protective measures can be taken,

- Avoid the blackened or burned parts of meat
- Eat grilled meat less frequently and eat smaller portions
- Flip meat frequently while grilling
- Cook meat in a microwave for one to two minutes before grilling (this pours off the juices and can remove 90% of HCAs)

http://www.foodsafetynews.com/2011/05/reducing-risk-when-grilling-meat/

25. Eating Yogurt May Reduce Colorectal Cancer Risk (May 23/11)

This prospective study on 45 241 (14 178 men; 31 063 women) volunteers of the EPIC-Italy cohort showed that men and women whose intake of yogurt was in the highest tertile were 38% less likely to be diagnosed with colorectal cancer when compared to those whose intake of yogurt was in the lowest tertile. The association was based on data collected through a dietary questionnaire that included yogurt consumption. Because the possible risk reduction was still 35% even after adjustment for other possible risk factors, the researchers suggested that yogurt should be part of a diet to prevent colorectal cancer.

Pala, V., et al. Yogurt consumption and risk of colorectal cancer in the Italian EPIC cohort. International J of Cancer. Published online. Doi: 10.1002/ijc.26193

26. Anti-Cancer Grilling Tips (Jun.10/11)

According to the health education manager at the University of Texas' Anderson Cancer Prevention Center, the following measures can be taken to reduce the risk of colorectal cancer while grilling on the BBQ in the summer,

- *Skip processed meats altogether* - Research shows processed meats like pastrami, hot dogs, pepperoni, bacon, ham and sausage can lead to DNA damage that promotes colorectal cancer.
- Consider grilling *fruits and vegetables*, combined with *fish*, instead of red meats.
- Keep consumption of red meat to *3 six ounce servings per week*. Also choose lean meat and trim fat before grilling.
- *Avoid burning and charring* - Grilled, burned and charred meats, including fish, form heterocyclic amines (HCAs) that also damage genes and can lead to cancer of the stomach and colon. Limit grilling time by cooking in the microwave first and cook at lower temperatures.
- *Marinade before grilling* - marinating meat with herbs, vinegar and lemon juice before grilling (for just 30 minutes) can reduce cancer causing HCA's by as much as 96 percent.

http://www.emaxhealth.com/1020/anti-cancer-grilling-tips-offered-experts

27. Colorectal Cancer Risk in Offspring Reduced by Vitamin B in Mom's Diet (Jun. 9/11)

Epidemiological data and animal studies have suggested a protective role for dietary folate and related B vitamins against colorectal cancer. In this study, researchers sought to determine the effect of folate and vitamin B availability during fetal life and the suckling period on intestinal tumorigenesis. Female wildtype mice were fed diets either mildly deficient, replete or supplemented with vitamins B(2), B(6), B(12) and folate for 4 weeks prior to mating. The females remained on their diets throughout pregnancy and until weaning. Results at 8 months showed that the tumour incidence among the offspring of supplemented mothers was 21%, compared with 59% for mothers who did not undergo supplementation and 55% for those whose mothers were deficient. The results also showed that tumours arising in the offspring of deficient mothers were more likely to be invasive. The authors therefore concluded that “maternal B vitamin supplementation may not only protect offspring against birth defects but also against colorectal cancer in adulthood”.

Ciappio, E.D., et al. Maternal B vitamin supplementation from preconception through weaning suppresses intestinal tumorigenesis in Apc1638N mouse offspring. Gut 2011.