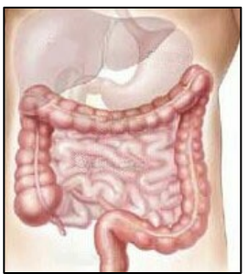
COLORECTAL CANCER RESEARCH UPDATES

Month Ending January 13th, 2012



The following colorectal cancer research update extends from November 19th, 2011 – January 13th, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Temporary Blood Pressure Drop After Receiving Avastin May Be Predictive Marker (Nov. 29/11)

This study sought to determine if a blood pressure drop after receiving Bevacizumab (Avastin) was associated with a longer disease free survival (time before the disease got worse). Blood pressure was measured 81 advanced colorectal cancer patients at 0, 90 and 180 minutes after receiving Avastin after 162 administrations of the drug. Twenty five patients (approximately 30%) demonstrated an average temporary drop of 20 mm Hg or more in their systolic blood pressure. The disease free survival in these patients was, according to the study authors, significantly longer than in the rest of the patients (291 days vs. 162 days respectively). The authors suggest that a temporary blood pressure drop after Avastin administration could be a predictive marker for Avastin treatment.

Kanai, M, et al., Temporary Blood pressure drop after bevacizumab administration is associated with clinical course of advanced colorectal cancer. British J Cancer. 2011 Oct. 27; 105: 1693-1696

2. Disease Free Survival Is Higher For Patients with Defective Mismatch Repair (dMMR) on Folfox (Dec. 1/11)

In this study, scientists reviewed clinical and tissue information from 303 stage III colon cancer patients who were treated with FOLFOX after surgery in 9 French hospitals over a 5 year period. About 1 in 10 (11.2%) had tumors with defective mismatch repair (dMMR) discovered either by analyzing markers for microsatellite instability or immunohistochemistry for missing proteins involved in dMMR. *For an explanation of MMR, please see Item #21 in this document.* Three years after surgery 90.5% of dMMR patients were alive and cancer-free compared to 73.8% of patients with proficient mismatch repair (pMMR). The study authors concluded that mismatch repair status is an independent prognostic biomarker for disease-free survival in patients with stage III colon cancer receiving adjuvant FOLFOX chemotherapy.

Zaanan, Aziz, et al., Defective mismatch repair status as a prognostic biomarker of disease-free survival in stage III colon cancer patients treated with adjuvant folfox chemotherapy. Clin Cancer Res, December 1, 2011. 17: 7470.

3. Molecular Markers as Predictors of Resistance to Anti-EGFR Therapies (Dec. 1/11)

Patients with advanced colorectal cancer and a mutation in the KRAS gene found in their primary tumour generally do not benefit from anti–epidermal growth factor receptor (EGFR) therapies such as cetuximab (erbitux) and panitumumab (vectibix). Yet, a large proportion of patients with KRAS wild-type tumors (tumours that do not have the genetic mutation) – accounting for approximately 40%–70% - also do not benefit from anti-EGFR targeted agents. In this study, investigators chose four molecular markers for analysis as potential predictors of resistance to anti-EGFR therapy:

- Human epidermal growth factor receptor–3 **(HER3)**,
- Insulin-like growth factor–1 **(IGF1)**,
- EGFR gene copy number **(GCN),** and
- Nuclear factor-kB **(NF-kB).**

Tumor samples were retrospectively collected from 168 patients with colorectal cancer treated with cetuximab and irinotecan after failure of irinotecan-based chemotherapy; 90 patients (54%) had KRAS wild-type tumors.

- **HER3**: In approximately half (51%) of the 90 patients, the KRAS wild-type tumors were HER3-positive, and in 49% were HER3-negative. The patients with HER3-negative tumors had significantly better outcomes in terms of response rate (50% partial response vs 25% for HER3-positive patients; median progression-free survival (PFS; 7 months vs 3 months;), and median overall survival (OS; 25 months vs 11 months;).
- **IGF1**: Similarly, outcomes were significantly improved in the patients with IGF1-negative tumors (n = 31) compared with those with IGF1-positive tumors (n = 59). A total of 20 (65%) patients with IGF1-negative tumors responded vs 13 (22%) of patients with IGF1-negative tumors. Median PFS was 9 months vs 2.5 months, and median OS was 25 months vs. 8 months.
- **NF-kB**: Patients with NF-kB–negative tumors (n = 32) had significantly better partial response rates (56% vs 26%), median PFS (7 months vs 3 months), and median OS (18 months vs 11 months), compared with patients whose tumors expressed NF-kB (n = 48).
- **GCN**: Finally, EGFR GCN was >2.12 in 43 patients and <2.12 in 47. Patients with EGFR GCN >2.12 had better partial response rates (37% vs 6%), longer median PFS (6 months vs 3 months), and longer median OS (18 months vs 10 months).

An analysis revealed that HER3-negative, IGF1-negative, and EGFR GCN >2.12 tumors were independently associated with increased response rate, whereas NF-kB–negative tumors were not. HER3-negative and IGF1-negative tumors also were independently correlated with improved PFS, whereas EGFR GCN >2.12 and NF-kB–negative tumors were not. For OS, HER3-negative, IGF1 negative, and EGFR GCN >2.12 tumors had an independent association with better outcome, whereas NF-kB–negative tumors did not. Study authors concluded that their analysis showed that a "favorable" tumor molecular pattern consisted of HER3 negative, IGF1 negative, or EGFR GCN >2.12. The patients with a favorable pattern had significantly improved median PFS (6 months vs 2.5 months) and median OS (16 months vs 6 months), compared with the patients with an unfavorable tumor molecular profile (ie, HER3 positive, IGF1 positive, and EGFR GCN <2.12). The authors do not that PFS and OS results in the patients with unfavorable-profile KRAS wild-type tumors did not differ significantly from those seen in patients with the KRAS-mutation.

Scartozzi, M, et al., analysis of HER-3, insulin growth factor-1, nuclear factor-kB and epidermal growth factor receptor gene copy number in the prediction of clinical outcome for kras wild-type colorectal cancer patients receiving irinotecan-cetuximab. Ann Oncol, 2011 Nov.23. Epub ahead of print.

4. Treating Peritoneal Carcinomatosis from Colorectal Cancer with Systemic Chemotherapy Does Not Have Ideal Outcomes (Dec. 14/11)

According to the results of this study, for patients with metastatic colorectal cancer (mCRC), ***peritoneal carcinomatosis colorectal cancer (pcCRC)*** is associated with significantly shorter overall survival (OS) and progression-free survival (PFS – time till the disease gets worse). Peritoneal carcinomatosis colorectal cancer is the widespread presence of colorectal cancer in the peritoneum, the lining of the abdominal cavity. The study investigators looked at the outcomes in patients with pcCRC who were enrolled into two prospective randomized trials of chemotherapy, and compared their outcomes with those of other manifestations of mCRC (non-pcCRC group). In total, 2,095 participants were enrolled (364 of whom had pcCRC) and assessed for OS and PFS. The investigators found that the pcCRC and non-pcCRC groups had similar characteristics with respect to median age, gender, and performance status, and significantly different characteristics with respect to the frequency of liver metastases (63% and 82%, respectively) and lung metastases (27% and 34%, respectively). Compared to the non-pcCRC group, the *pcCRC group had significantly shorter median OS* (12.7 versus 17.6 months) and PFS (5.8 versus 7.2 months). Even after adjusting for age, performance status, liver metastases, and other factors, pcCRC had an unfavorable prognostic influence which was significant. For both pcCRC and non-pcCRC patients, first line of treatment with infusional fluorouracil, leucovorin, and oxaliplatin (folfox) was significantly better than irinotecan, leucovorin, and fluorouracil (folfiri). The study authors concluded "pcCRC is associated with a significantly shorter OS and PFS as compared with other manifestations of mCRC".

Franko, Jan, et al., Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J of Clin Onc. Published online before print Dec 12, 2011, doi: 10.1200/JCO.2011.37.1039

5. Oxaliplatin-Induced Neuropathy in Colorectal Cancer (Oct. 20/11)

Oxaliplatin use in palliative and adjuvant treatment of colon cancer is frequently limited by cumulative neurotoxicity (characterized by the numbness and tingling in the hands and feet), leading to reduced quality of life and decreased dose. Various preventative measures have been tested to reduce the incidence of neurotoxicity, including calcium and magnesium infusions, dose interruption of the drug, and prophylactic neuromodulatory agents. Despite the promising efficacy of these measures, they are not universally accepted. Less is known about the best way to treat established neurotoxicity, which is permanent in some patients, although ***venlafaxine*** has shown promise in small clinical trials. This study analyzes the extent, cause and risk factors for neuropathy, and the potential preventative and therapeutic treatments for oxaliplatin-induced neuropathy. To read the study in its entirety, please click on the following link: http://www.hindawi.com/journals/jo/2011/201593/

Weickhardt, Andrew, et al., Oxaliplatin-induced neuropathy in colorectal cancer. J of Onc. Vol. 2011, Article ID 201593

6. **Jennerex Announces First Patient Treated in Phase 2a Clinical Trial Involving JX-594** (Dec.21/11)

The first patient has been treated in a Phase 2a clinical trial of JX-594 as a neoadjuvant therapy in patients who are undergoing surgery to treat colorectal cancer that has spread to the liver. The study is being led by Rebecca Auer, M.D., surgical oncologist at The Ottawa Hospital, associate scientist at the Ottawa Hospital Research Institute and assistant professor of surgery at the University of Ottawa in Ottawa, Canada. The clinical trial is being supported by funding from the Ontario Institute for Cancer Research. This Phase 2a clinical trial will enroll approximately 20 patients with colorectal cancer metastases to the liver. Patients will receive a single injection of JX-594 intravenously or intratumorally two weeks prior to surgical resection. Tumors will be evaluated for evidence of JX-594 replication and pathologic response. Patients will subsequently be followed for progression-free survival and overall survival. For more information about the trial, please visit www.clinicaltrials.gov. JX-594 is a proprietary, engineered oncolytic virus that is designed to selectively target and destroy cancer cells. JX-594 is

designed to attack cancer through three diverse mechanisms of action: 1) the lysis of cancer cells through viral replication, 2) the shutdown of the blood supply to tumors through vascular targeting and destruction, and 3) the stimulation of the body's immune response against cancer cells, i.e., active immunotherapy. Phase 1 and Phase 2 clinical trials in multiple cancer types to date have shown that JX-594, delivered either directly into tumors or systemically, induces tumor shrinkage and/or necrosis and is well-tolerated by patients (over 120 treated to date). Objective tumor responses have been demonstrated in a variety of cancers including liver, colon, kidney, lung cancer and melanoma. JX-594 has had a favorable safety profile to date with predictable and generally mild side effects that typically include flu-like symptoms that resolve in 24 to 48 hours.

http://www.jennerex.com/pr_122111.html

7. Phase 2 Trial Testing Tivozanib in Combination with Folfox6 (Dec.22/11)

Aveo Pharmaceuticals has launched a Phase 2 trial to test its cancer drug candidate ***tivozanib***, in combination with FOLFOX6 and evaluated versus Avastin, as first line therapy in patients with advanced colorectal cancer. This new trial, called **BATON-CRC**, is part of a series of trials designed to discover whether tivozanib could work especially well in patients with certain genetic biomarkers. It has begun enrolling participants and plans to include approximately 252 patients with no prior VEGF-targeted therapy at about 80 centers in the U.S., Canada, Australia and Europe. Patients will be randomized to one of the two treatments arms in a 2:1 ratio (168 patients in the tivozanib arm and 84 patients in the bevacizumab arm). One component of BATON-CRC is the assessment of biomarker relationships that may be predictive of response, including lactate dehydrogenase (LDH). LDH is a protein that normally appears throughout the body in small amounts and can be elevated in patients with certain cancers, including colorectal cancer. Measuring LDH levels can be helpful in monitoring cancer treatment and determining patients' response to therapy. For additional information, please visit www.clinicaltrials.gov. Tivozanib is a potent, selective and continuous inhibitor of all three vascular endothelial growth factor (VEGF) receptors that is designed to optimize VEGF blockade while minimizing toxicity to the rest of the body not containing tumours. Tivozanib is an oral, once-daily, investigational tyrosine kinase inhibitor that is in a Phase 3 clinical study in advanced renal cell carcinoma, and is also being evaluated in other tumors.

http://investor.aveopharma.com/phoenix.zhtml?c=219651&p=irol-newsArticle&ID=1642195&highlight

8. Results of a Phase 2 Study Involving Enzastaurin And Avastin After First Line Therapy for mCRC (Jan.6/12)

Enzastaurin and bevacizumab (Avastin) have demonstrated synergistic antitumor effects and, in phase 1 studies, the combination was well tolerated. This phase 2 study assessed enzastaurin with 5-fluorouracil/leucovorin plus bevacizumab as maintenance therapy for metastatic colorectal cancer (MCRC). Patients with locally advanced or MCRC and stable or responding disease after completing 6 cycles of first-line chemotherapy randomly received enzastaurin followed by subsequent doses or placebo. Both arms received 5-fluorouracil/leucovorin plus bevacizumab, every 2 weeks. The primary endpoint was progression-free survival (PFS), from randomization. Overall survival (OS) and PFS were also assessed from start of first-line therapy. Enrollment was stopped, and the final analysis was conducted after 73 PFS events. After analyzing the results, investigators concluded that enzastaurin combined with bevacizumab-based therapy is tolerable, but does not improve PFS during maintenance therapy in patients with MCRC compared with bevacizumab-based therapy alone.

Wolff, R.A., et al., A double blind randomized placebo controlled phase 2 study of maintenance enzastaurin with 5 fluorouracil/leucovorin plus bevacizumab after first-line therapy for metastatic colorectal cancer. Cancer, doi: 10.1002/cncr.26692

9. Primary Colorectal Cancers and Their Subsequent Hepatic Mets Are Genetically Different (Jan. 11/12)

In the era of DNA-guided personalized cancer treatment, it is essential to perform predictive analysis on the tissue that matters. Here investigators analyzed genetic differences between primary colorectal adenocarcinomas (CRCs) and their respective metastasis. In this study, the primary CRC and the subsequent hepatic metastasis of 21 CRC patients were analyzed. On average 83 potentially function-impairing variations were gained in the liver metastasis and 70(SD 48) variations were lost, showing that the primary tumor and hepatic metastasis are genetically significantly **different**. Besides novel and known variations in genes such as KRAS, BRAF, KDR, FLT1, PTEN, and PI3KCA, differences in the up-/downstream genes of EGFR/PI3K/VEGF-pathways and other pathways (mTOR, TGFbeta, etc.) were also detected, potentially influencing therapeutic responsiveness. Chemotherapy between removal of the primary tumor and the metastasis (N=11) did not further increase the amount of genetic variation. The study results indicate that the ***genetic characteristics of the hepatic metastases are different from those of the primary CRC tumor.*** As a consequence, the choice of treatment in studies investigating targeted therapies should ideally be based on the genetic properties of the metastasis rather than on those of the primary tumor.

Vermaat, Joost S., et al., Primary colorectal cancers and their subsequent hepatic metastases are genetically different: implications for selection of patients for targeted treatment.

10. **Phase II Clinical Trial Involving Pentamidine for mCRC Patients Undergoing Second Line Therapy** (Jan.13/12)

The purpose of this study is to investigate the safety and efficacy of the use of OCZ103-OS or Pentamidine in combination with standard of care (folfiri or folfox) for metastatic colorectal cancer patients with disease progression following a first line treatment. The objectives of the study are:

- To assess the efficacy of OCZ103-OS in prolonging overall survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.

- To assess the efficacy of OCZ103-OS in prolonging progression free survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.

For more information, please visit http://www.colorectal-cancer.ca/en/research-treatments/listing-trials/ or visit the Oncozyme website at:
http://www.oncozymepharma.com/index.php?option=com_content&view=article&id=5&lang=en

http://www.oncozymepharma.com/index.php?option=com_content&view=article&id=5&lang=en

SURGICAL THERAPIES

11. Liver Resection and Resection of Concurrent Extrahepatic Disease is Reviewed (Jan. 11/12)

Recent data suggest that hepatectomy (surgical resection of the liver) for patients with colorectal liver metastases (CLM) with concurrent extrahepatic disease (EHD) achieve encouraging survival results. The authors examined the clinical efficacy of this treatment approach through a systematic review of the published literature from January 2000 to January 2011. They identify studies reporting outcomes of hepatectomy for CLM where resection of EHD was undertaken. Twenty-two studies were examined. This comprised 1142 patients. The median disease-free survival was 12 months, median overall survival was 30 months and median 5-year survival rate was 19%. Median 5-year survival of patients with complete hepatectomy with resection of EHD was 25%. Survival based on site of EHD includes:

- lung; median survival (M/S) was 41 months,
- porto-caval lymph node; M/S was 25 months,
- peritoneal metastases; M/S was 25 months.

The authors maintain that in the era of effective systemic therapies, surgical resection of CLM and concomitant EHD in carefully selected patients may achieve survival results superior to non-surgically treated patients. This treatment strategy may be considered appropriate especially when a R0 hepatectomy (complete resection with no microscopic residual tumor) and complete resection of EHD may be achieved.

Chua, TC, et al., Hepatectomy and Resection of Concomitant Extrahepatic Disease for Colorectal Liver Metastases—A Systematic Review. Eur J Cancer. 2011 Dec 7;[Epub Ahead of Print]

RADIOTHERAPY / INTERVENTIONAL RADIOLOGY

12. Chemoradiation Only for Rectal Cancer (Nov. 21/11)

Neoadjuvant chemoradiotherapy (CRT – chemoradiotherapy given before surgery) for locally advanced rectal cancer may result in a pathologic complete response (pCR) in resected tissue, raising the intriguing possibility that some patients might be able to forego surgery altogether. A previous study demonstrated high survival rates in patients with low rectal cancer who achieved a clinical complete response (cCR) after CRT. The present study evaluated outcomes of no surgery combined with intensive follow-up (wait-and-see policy) in patients with cCRs after CRT, and evaluated the use of magnetic resonance imaging (MRI) in selection and follow-up of these patients. Patients with rectal cancer who had a cCR after CRT were given the choice of total mesorectal excision (TME surgery) or a wait-and-see protocol, with the caveat that TME was the standard treatment with the best control, and that wait-and-see was experimental and controversial. These patients were included in this study as well as patients who were enrolled in a prospective cohort study. Primary staging was conducted using MRI. Patients with local advanced rectal cancer were to receive CRT, which consisted of radiotherapy combined with capecitabine (better known as xeloda). For patients in the wait-and-see group, follow-up consisted of digital rectal examination, MRI, endoscopy with biopsy, computed tomography (CT) scans of the chest and abdomen, and measurement of carcinoembryonic antigen (CEA). Adjuvant therapy (therapy administered after surgery) consisted of oxaliplatin and capecitabine administered during six 3-week cycles. A total of 192 patients received CRT, of whom 21 had a cCR and were followed via the wait-and-see policy. Mean follow-up was 25 months. The control group comprised patients who had a pCR after

CRT and TME. Among the patients in the wait-and-see group, 10 (50%), had distal tumors that would have required abdominoperineal resection with permanent colostomy. Of the 10 patients, 1 had inflammation that required surgery after 14 months of follow-up. Of the patients in the pCR control group, 9 required a definitive colostomy and 11 required temporary colostomy. Major complications occurred in 35% of these patients, and minor complications occurred in 15% of them. Patients in the pCR group had worse bowel function after surgery than was observed in the wait-and-see group. Of the patients in the wait-and-see group, 1 developed a small endoluminal local recurrence (T1 tumor) after 22 months of follow-up; the other 20 are currently alive and disease-free. The cumulative probability of 2-year disease-free survival (DFS) was 89% and cumulative probability of 2-year overall survival (OS) was 100%. In the pCR control group, 2 patients died, 1 of complications associated with colostomy closure surgery and 1 of metastatic disease. The cumulative probability of 2-year DFS was 93% and cumulative probability of 2-year OS was 91%. The groups did **not differ** in cumulative probabilities of DFS and OS.

Maas, M, et al., Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer. J Clin Oncol. 2011 Nov 7;[Epub Ahead of Print],

13. Using PET/CT for Early Outcome Prediction in Patients with mCRC Undergoing Chemo (Dec.14/11)

Assessment of objective response is crucial to evaluate the benefit of treatment (chemo and biologics) for solid tumors, relying on size criteria determined by morphologic imaging such as CT scans. This may require waiting 6 to 8 weeks while patients are receiving therapy, exposing them to the risk of developing toxic effects in case of treatment failure. According to the study authors, ***metabolic changes in cellular energy associated with tumor shrinkage during chemotherapy should predict treatment response earlier than changes in tumor size***. This study was conducted to assess the predictive value of 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)/computed tomography (CT) metabolic response after one course of chemotherapy in patients with metastatic colorectal cancer (mCRC). Eligible patients were scheduled to receive chemotherapy for mCRC and were enrolled in the study before receiving their first treatment. Patients were required to have at least one metabolically measurable lesion >15 mm in diameter with a marked FDG accumulation. A baseline (BL) CT scan was required <2 weeks before the first course of chemotherapy, and follow-up CT scans were performed after three courses of treatment. FDG–PET/CT scans were performed at BL and on day 14 after one cycle of chemotherapy, with the goal of assessing the predictive value of early FDG–PET changes on objective tumor response and treatment outcome. The metabolic assessment process consisted of identifying target lesions, assessing the metabolic response of each target lesion, and evaluating overall metabolic response. Patient outcomes (secondary endpoints) were progression-free survival (PFS), defined as the time between early response FDG–PET/CT scan and radiologic documentation of progression or date of death, and overall survival (OS), defined as the time between early response FDG–PET/CT scan and date of death. Patient follow-up was up to 28 months. Of the 40 eligible patients, 23 (58%) showed metabolic response 2 weeks after the first treatment cycle. In metabolically responding patients, a radiologic response was seen in 10 (43%) of 23, compared with 0 (0%) of 17 in metabolically non-responding patients. The results of this study demonstrated that FDG uptake changes seen in patients with mCRC after receiving one course of chemotherapy can be useful as a prognostic marker to predict failure of the treatment to induce a morphologic response. In this study, early metabolic assessment appeared to correlate with overall prognosis, with responding patients showing significant survival benefit over nonresponders. **The ability to identify patients with non-responding metastatic disease early in treatment will allow the physician to stop ineffective treatments quickly. These findings may have significant impact on future clinical management of patients with mCRC or other solid tumors.**

Hendlisz, A, et al., Serial FDG–PET/CT for Early Outcome Prediction in Patients With Metastatic Colorectal Cancer Undergoing Chemotherapy. Ann Oncol. 2011 Nov 23;[Epub Ahead of Print],

14. Trans-Arterial Chemoembolization for Colorectal Liver Mets (Dec.23/11)

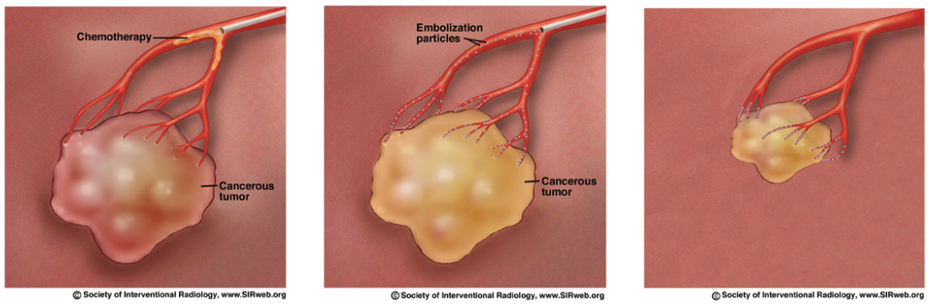
According to the study authors, trans-arterial chemoembolization (TACE) is a promising locoregional therapy for the treatment of primary hepatic tumors and liver metastases. The aim of the study was to define the activity and outcome of using DC Bead, drug-eluting bead, a spherical embolic device capable of being loaded with irinotecan. Investigators conducted a double institutional, single arm, phase II clinical study to evaluate TACE adopting this device in 82 patients presenting with metastatic colorectal carcinoma to the liver after failing chemotherapy. The primary endpoints were tumor shrinkage, safety, feasibility, compliance, and overall survival. Out of 103 patients considered, 82 were enrolled and underwent a total of 185 treatments of TACE. The median number of TACE was 2.2. A post-embolization syndrome was frequently observed. Adverse observed effects were:

- right upper quadrant pain (40%),
- fever (80%),
- nausea (27%) and
- increased transaminases (70%).

The median follow-up was 29 months. Within one month after treatment, each patient received a computed tomographic scan. It showed reduction of metastatic contrast enhancement in all patients. Responses were 78% at 3 months. After the first treatment, 75 of 82 patients declared an improvement of their well being lasting more than 18 weeks. The median duration of response was 6 months; the median follow up was 29 months. The median survival was 25 months, with progression free survival at 8 months. Study authors suggest that TACE adopting DC Bead®, drug-eluting bead loaded with irinotecan could be proposed as palliative therapy for unresectable and chemotherapy resistant liver metastases from CRC.

Trans-arterial Chemoembolization

Chemoembolization delivers a high dose of cancer-killing drug (chemotherapy) directly to the organ while depriving the tumor of its blood supply by blocking, or embolizing, the arteries feeding the tumor. Using imaging for guidance, the interventional radiologist threads a tiny catheter up the femoral artery in the groin into the blood vessels supplying the liver tumor. The embolic agents keep the chemotherapy drug in the tumor by blocking the flow to other areas of the body. This allows for a higher dose of chemotherapy drug to be used, because less of the drug is able to circulate to the healthy cells in the body. Chemoembolization usually involves a hospital stay of two to four days. Patients typically have lower than normal energy levels for about a month afterwards.



Source: ***http://www.idahoarteryandvein.com/treatments/chemoembolization.php***

Alberti, Camillo, et al., Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead, drug eluting bead loaded with irinotecan: results of a phase II clinical study. Anticancer Research. December 2011. Vol. 31, No. 12: pp. 4581-4587

SCREENING

15. Flexible Sigmoidoscopy Does Not Significantly Increase Polyp & Cancer Detection When Used with CT Colonography (Virtual Colonoscopy) (Dec.29/11)

According to the study authors, flexible sigmoidoscopy (FS) increases polyp and cancer detection in addition to double contrast barium enema (DCBE). However, CT colonography (CTC) is now the preferred technique. The aim of the study was to explore whether FS increases polyp and cancer detection rates when used in addition to CTC. Patients who underwent FS and CTC between 2007 and 2009 were included and data were collected from patient records. Yields of polyp, adenoma and carcinoma detection were calculated for FS and CTC. In a cohort of 294 patients, CTC detected 36 patients with carcinomas while FS detected 28. One rectal cancer not seen on CTC was diagnosed by FS. Polyps were seen by CTC in 66 and FS in 45 patients. In 5 patients FS found polyps that were not detected by CTC; 3 of which were small adenomas. FS detected extra adenomas or carcinomas in 1.36% (4/294). Adding FS to CTC neither increased the cancer nor the polyp detection yield significantly. The authors concluded that this first study investigating the use of FS in addition to CTC detected little additional pathology. The routine use of FS as a supplement to CTC for adenoma and carcinoma detection is of questionable utility.

Virtual Colonoscopy

The exam requires a less vigorous preparation, does not require sedation, is much less invasive and provides minimal disruption to a patient's daily routine. Rather than drinking the large amount of fluid required by some colonoscopy preps, virtual CT colonoscopy requires only 12 ounces of liquid prep and a clear liquid diet the day before the exam. Patients may even enjoy their morning cup of coffee before undergoing a virtual CT colonoscopy since no sedation is needed. Patients experience minimal discomfort during the exam, which takes just a few minutes. A small straw is inserted, gas is instilled with a special machine to avoid cramping, and the CT images are obtained. Patients can eat breakfast and resume normal activities, including work, immediately following the procedure.

Virtual CT colonoscopy creates 3D images of the entire colon and a complete CT scan of the abdomen and pelvis, which can detect kidney stones, gallstones, aneurysms and tumors at an early stage before they cause symptoms. A 3D virtual view of the colon is also obtained. Unlike traditional colonoscopy, which requires the camera to go through the colon with the aid of an endoscope, the 3D computer creates these images. The computer measures polyps or abnormalities that may be detected.

Source: *http://www.mdnews.com/news/2011_12/05788_decjan2012_colon-cancer-detection*

Selinger, CP, et al., Flexible sigmoidoscopy does not significantly increase polyp and cancer detection yield when used to supplement CT colonography. Digestion: Intl J of Gastro. Vol. 85, No. 1, 2012.

OTHER

16. Aspirin on Cancer Risk in Carriers of Hereditary Colorectal Cancer (Nov. 29/11)

According to the results of this study, chemoprevention with aspirin cut development of colorectal cnacer by 60% in patients at high risk for the disease because of a genetic defect. Relative to placebo, the risk of developing colorectal cancer was cut by 60% in carriers of Lynch Syndrome when they took 600mg/day of aspirin for at least two years and were followed for up to 11 years. Patients with Lynch Syndrome are estimated to account for about 3% of all colorectal cancer cases. The current study, called CAPP2 randomized 661 individuals with Lynch syndrome to take daily aspirin or placebo for up to four years. Lynch Syndrome involves loss-of-function mutations in a DNA mismatch repair gene. These mutations are rare, but approximately 80% of individuals with them will develop colorectal cancer eventually. Cancers of Lynch syndrome patients also tend to develop at an earlier age than sporadic tumors. As a result, the CAPP investigators believed a chemoprevention study could be conducted more economically in Lynch syndrome patients than in the general population, requiring fewer participants and a shorter time necessary to see a treatment effect. It should be noted that for participants who took aspirin for less than two years, there was no apparent benefit.

Burn, J, et al., Long term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomized controlled trial. Lancet 2011: DOI: 10.1016/SO140-6736(11)61049-0

17. Report on Cancer Survival Rates (Nov.22/11)

Survival rates have risen dramatically for many types of cancer but have hardly improved for others, according to figures released by the cancer charity Macmillan in the U.K. Macmillan's new report highlights the massive improvements that have been made in some areas. For example, people diagnosed with colon cancer might typically live beyond a decade, compared to just seven months if they had been diagnosed 40 years ago. However, it appears there is a major need to boost survival rates for lung cancer, pancreatic cancer and stomach cancers, which have hardly improved despite 40 years of medical advances. The report was compiled by Macmillan Cancer Support to estimate how long people lived on average after they were diagnosed with various types of cancer. Figures were calculated for people diagnosed at various times from 1971 to 2001, and the expected average life expectancy for people diagnosed in 2007 was predicted. Cancer survival rates are typically presented as the percentage of patients that will still be alive five or ten years after diagnosis. Instead, this report used historic data to estimate how long on average people would currently live after diagnosis and whether this had improved in the past four decades. The estimated average survival times for people diagnosed in 1971–72 and 2007 respectively were:

- **adult leukaemia –** 4 months (1971–72) and 36 months (2007)
- **ovarian cancer –** 8 months and 37 months
- **myeloma** (a type of blood cancer that can also affect bone tissue) **–** 5 months and 30 months
- **stomach cancer –** 2 months and 8 months
- **oesophagus (foodpipe) cancer –** 2 months and 8 months
- **brain cancer –** 3 months and 7 months
- **pancreatic cancer –** 2 months and 3 months

- **lung cancer –** 3 months and 5 months
- **kidney cancer –** 9 months and 64 months
- **rectum cancer –** 15 months and 106 months
- **colon cancer –** 7 months and 120 months
- **non-Hodkin's lymphoma and "other cancers" –** 12 months and 120 months

The report calculated these estimates as "median survival times" for different types of cancer. This means the length of time after diagnosis until half of the people with that type of cancer have died. Macmillan says some patients may want to know this statistic to answer the common question of how long someone can expect to live after their diagnosis. While this may be useful, it is important to note that this figure is an average, and half the people would be expected to live longer than this estimated "life expectancy". Also, outcomes for certain cancers can vary greatly depending on the stage at which cancer is first detected and the types of treatment this will allow. For example, there are generally better options for treating a cancer detected early using screening or early diagnosis techniques than one detected later due to problematic symptoms. The largest improvements have been for ***colon cancer (17-fold increase in median survival).*** Non-Hodgkin's lymphoma showed a 10-fold increase, and ***rectal cancer showed a seven-fold increase.*** The report highlighted that although it is good news that more cancer patients are living longer overall, they may not be spending this time living well. It points out that "cancer treatment is the toughest fight many people will face and patients are often left with long-term health and emotional problems long after their treatment has ended". Macmillan illustrates this point by highlighting that although colorectal cancer is one of the cancers with large improvements in median survival time, 64% of people still alive five to seven years after their diagnosis have an ongoing health problem.

http://www.newsletter.co.uk/news/health/cancer_survival_still_varies_greatly_1_3286390

18. Everist Genomics Discovers Genes Responsible for CRC Recurrence (Dec.6/11)

For decades, patients diagnosed with early-stage colorectal cancer believed they were relatively fortunate; that is, the disease has been caught early; treatment with surgical removal of the tumor alone will suffice; they won't need adjuvant chemotherapy; and their prospects for beating the disease are very good. This view was driven by the assumption that all early-stage colorectal cancer tumors were 'low-risk' for recurrence. However, recent studies have revealed that these assumptions were based on an incomplete understanding of early-stage colorectal cancer, namely, that some types of early-stage tumors are much more deadly than others. Recurrence and mortality rates associated with early-stage colorectal cancer are, in fact, much higher than previously realized. Nearly one in three patients with Stage 2 colon cancer that have undergone surgical removal of their tumor alone will have a recurrence of their cancer, and over 80% of those that do recur will die from their disease. We now know that patients with 'high-risk' early-stage colorectal cancer are up to 29X more likely to have a recurrence of their tumors than patients with low-risk disease. More specifically, in a recently completed study involving 291 colorectal cancer patients, fewer than 3% of patients identified with low-risk tumors experienced a recurrence of their cancers compared to a staggering 68% recurrence rate in patients with high-risk early-stage disease. What if there were a test that would accurately identify patients with early-stage high-risk tumors and treat these patients with surgical removal of their tumor and add chemotherapy? The scientific team at Everist Genomics identified research which revealed that patients with high-risk Stage 2 colorectal tumors can benefit greatly from adjuvant therapy, with 3-year disease-free survival rates increasing from 84.7% in patients that did not receive chemotherapy to 96.4% in those that did. Improvements in 5-year overall survival rates increase from 86.4% to over 98%. These insights led the scientists at Everist Genomics to commence a 2-year development program to discover the combination of genes and their expression levels that would identify patients with these high-risk early-stage colorectal cancer tumors. The genomic culprits turned out to be a combination of **5 specific genes** and gene expression levels. If they are present in a patient's early-stage colorectal cancer tumor, then it's a high-risk tumor. Based on these insights, Everist Genomics (stationed in Michigan, USA) has created the world's only molecular diagnostic test, **OncoDefender-CRC**, capable of accurately identifying tumors at high risk for recurrence amongst all early-stage (Stage I/II) colon and rectal cancers. OncoDefender-CRC testing is provided as a CLIA lab-based service. Everist Genomics made the OncoDefender-CRC test available commercially in November of 2011. During the first month of commercial availability, Everist Genomics has already fulfilled physician requests for over 1,000 OncoDefender specimen collection kits. Further supporting the clinical and financial merits of the test, Sanford Health Plan has established a reimbursement policy for OncoDefender-CRC, which will allow its members to receive coverage for the test beginning in January 2012. To obtain more information on OncoDefender-CRC, please click on the following link: http://www.everistgenomics.com/content/oncodefender/overview.htm .

Weinberg, T et al. Occult tumor burden predicts disease recurrence in lymph node-negative colorectal cancer. Clin Cancer Res 2011 (doi:10.1158/1078-0432.CCR-10-3113)

http://www.everistgenomics.com/content/media/releases/120611.htm

19. Researchers Link Epigenetic Changes to Inflammation-Induced Colon Cancer (Dec.8/11)

Johns Hopkins Kimmel Cancer Center scientists report that sharp rises in levels of reactive oxygen molecules, and the inflammation that results, trigger biochemical changes that silence genes in a pattern often seen in cancer cells. The researchers confirmed this gene-silencing effect in mice that develop

inflammation-induced colon cancer. This study is believed to be the first to identify a specific molecular mechanism *linking inflammation to cancer epigenetics*. Epigenetic changes alter the usual patterns of gene expression in cells and typically cause the silencing of tumor-suppressor genes. This finding could explain why epigenetic changes are found in cancer cells and one important reason inflammation is so frequently linked to cancer. In the past several years, researchers have noted that cancers linked to chronic inflammation, such as some colon tumors, appear to be enabled by early changes in patterns of DNA methylation, the addition of a molecule known as a methyl group to the "engine-starter" region of a gene known as a promoter. Methylation events reduce or completely shut down the gene's ability to make functional proteins. Cancer cells typically show abnormal patterns of DNA methylation. The study team exposed cells to high levels of hydrogen peroxide, a strongly reactive molecule known as a reactive oxygen species which is emitted by a variety of cells during episodes of inflammation. Hydrogen peroxide can damage DNA, as well as other proteins and structures within cells. The team found that peroxide-induced damage recruited methyltransferases to damage sites. The enzymes also appeared to form large, molecular complexes with other proteins involved in epigenetic gene-silencing. These effects did not appear when DNA was damaged by gamma or ultraviolet radiation, suggesting that they are largely a result of reactive oxygen damage induced by inflammation. The study team suspects that epigenetic silencing evolved to temporarily give inflamed tissue an opportunity to repair and renew itself. However, when inflammation becomes chronic and lasts too long, the silencing process may "become locked-in for some vulnerable genes." The loss of these genes may allow uncontrolled cell division and growth, bringing them one step closer to cancer. Chronic inflammation induced by viruses, bacteria, toxins and autoimmune processes is well known to promote common types of cancer, including colon, lung and liver cancer. It is the study team's hope that by understanding how inflammation brings about this abnormal epigenetic process, they might be able to use drugs to target it and thereby prevent many cancers.

http://www.medicalnewstoday.com/releases/238852.php

20. Colorectal Cancer is Rising in Those Under 50 (Dec.19/11)

Contrary to what is happening for people over fifty, rates of colon and rectal cancer are rising in younger adults. While new colorectal cancers in older people have fallen consistently since 1985, rates for people under 50 have risen, particularly for rectal cancer. Even more concerning, young people with colon cancer were diagnosed at later, less curable stages than those 50 or older. Almost two-thirds had a stage III or IV cancer compared to half of people diagnosed at a later age. In this study, researchers analyzed colon and rectal cancer cases in the National Cancer Database diagnosed in the ten years between 1999 and 2007. About 1 in 10 were diagnosed before the age of 50 — 64,068 of 588,869 in the total database. After 2001, there was an average annual increase of 2.1% in young onset colorectal cancer compared to a decrease of 2.5% yearly for those 50 and older. Rectal cancer increased even more rapidly in younger patients at an average annual change of 3.9%. The median age of younger patients was 44, with 3 out of 4 (75.2%) diagnosed in their forties. Cancer that had spread to either regional lymph nodes (stage III) or to distant organs (stage IV) occurred in:

- 63% of young colon cancer patients.
- 57.7% of young patients with rectal cancer

Compared to colorectal cancer in older patients, young-onset cancer occurred more often in:

- the rectum or the lower (distal) colon (69% vs 57.7%)
- patients who were uninsured or had Medicaid (16.5 % vs 4.7%)
- patients who lived in the south or western US (56.2% vs 50.3%)

Younger patients were also more likely to have mucinous or signet-ring subtypes and poor differentiation. The study authors concluded: *These data argue for heightened awareness of these concerning trends in young-onset CRC. Symptomatic young patients should undergo timely sigmoidoscopy at a minimum, if not a full colonoscopy. Identifying high-risk cohorts for targeted screening should be a priority.*

You, Nancy, et al., Young onset colorectal cancer: is it time to pay attention? Arch Intern Med. Published online December 12, 2011. Doi: 10.1001/archinternmed.2011.602

21. Understanding MMR Status for Stage II Colon Cancer Patients (Dec.26/11)

The MMR status of a patient's tumor provides additional information about a patient's individualized prognosis. Studies have shown that Stage II colon cancer patients with MMR-deficient (MMR-D) tumors have a lower risk of recurrence compared to patients with MMR-proficient (MMR-P) tumors. Knowing their MMR status may help Stage II colon cancer patients and their doctors make more informed decisions about how to best treat their disease.

In **MMR-P** tumors, an intact MMR pathway corrects errors in DNA replication that occur routinely during cell division. In **MMR-D** tumors, the MMR pathway is compromised and the errors are not corrected. Approximately 15% of stage II colon cancer patients have tumors that are MMR deficient. MMR deficiency is also observed in Lynch Syndrome, a hereditary form of colon cancer, though the majority of patients with MMR-D tumors do not have Lynch Syndrome. However, patients with MMR-D tumors

should speak with their doctors about further testing.

Recent studies have also suggested that patients with **MMR-D** colon cancer may be resistant to 5-FU based chemotherapy, but this remains an ongoing question of study. Taken together, these findings have led to the consideration of MMR testing for assessment of recurrence risk in select stage II colon cancer patients in the NCCN Colon Cancer clinical practice guidelines, although its clinical application to adjuvant treatment decision-making continues to evolve.

Tumor MMR status can be determined in two different ways:

1. Immunohistochemistry (IHC) to identify protein expression of known proteins in the MMR pathway or
2. DNA-based PCR analysis to assess the presence of microsatellite instability.

Both methods have been shown to be highly concordant, with concordance rates of up to 97% reported in the literature. Based on recent data, **Genomic Health** has begun providing MMR testing for recurrence risk assessment as part of the **Onco*type* DX** service in late 2011. The **Onco*type* DX colon cancer assay** is a colon cancer test that provides an individual, numerical assessment of how likely colon cancer is to return in patients with stage II colon cancer following surgery to remove the tumor. The multigene expression assay examines the activity of specific genes within a patient´s tumor sample in order to provide individualized information to each person and their physician about the specific biological make-up of their colon cancer. The Onco*type* DX assay is appropriate for people who are newly diagnosed with stage II colon cancer and is performed on tumor tissue removed during the original surgery. Because of this, the Onco*type* DX assay does not require any additional surgery or procedures in order for a patient to get the test. For detailed information about Onco*type* DX, please call: (866) ONCOTYPE or visit **www.oncotypedx.com.**

http://www.genomichealthupdates.com/fall11_04.html

22. Colorectal Cancer Does Not Form With DCC Gene (Dec.22/11)

Usually we hear about genetic mutations that can lead to cancer. New research has identified a gene that actually protects against cancer - a finding that could lead to the development of new drug therapies. Researchers have found that mice with a genetic defect in DCC (deleted colorectal cancer) develop cancer. This gene is designed to protect against cancer. Knowing the mechanisms behind how this works might offer a new target for drugs to keep this gene doing what it's supposed to do. The study investigators explored cell death, a process known as apoptosis. In particular, the researchers were looking to see what makes cells know they are to begin self destruction when they become abnormal. The team found the key seems to lie with sentinels on the surface of cells which examine their environment. Scientists have named these "dependence receptors." When a cell has a receptor that is associated with its ligand (a binding molecule), then all is well with the cell. But when the cell doesn't have its ligand, it sends a signal that it's time to die. In the case of cancer cells, when ligands are missing, the cells start killing themselves instead of growing chaotically. The study investigators uncovered all this by modifying the DCC gene in mice. The researchers learned that the gene protects against the onset of cancer because it causes the death of malignant cells. On the other hand, when the DCC "dependence receptors" are eliminated by mutation, the mice spontaneously developed colon cancer. The study authors say this tumor-suppressing gene naturally protects against cancer" "Unfortunately, certain cancer cells escape from this control by blocking this 'dependence receptor' mechanism. That is how we know that the DCC gene is extinguished in most human cancers". Future research will focus on developing targeted therapies that work on reactivating the death march of cancer cells to destroy several types of cancer. The study team has also come up with several candidate drugs and hopes to be able to conduct human clinical trials in several years.

Mehlen, Patrick, et al., DCC constrains tumour progression via its dependence receptor activity. Nature (2011). DOI: doi:10.1038/nature10708

23. Long Term Risk of CRC after Adenoma Removal (Jan.11/12)

Previous studies examining the incidence of colorectal cancer after polyp removal have provided some inconsistent findings. The aim of this study was to compare the risk of colorectal cancer after adenoma removal in routine clinical practice with the risk in the general population. Patients diagnosed for the first time with colorectal adenoma between 1990 and 1999 were included (n=5779). Initial and follow-up data until December 2003 were used to calculate the colorectal cancer **standardized incidence ratio** (SIR) and cumulative probabilities after adenoma removal. After a median follow-up of 7.7 years, 87 invasive colorectal cancers were diagnosed whereas 69 cases were expected. Compared with the general population, the overall SIR was 1.26. The risk of colorectal cancer depended on the characteristics of the initial adenoma SIR 2.23 for advanced adenomas and 0.68 for non-advanced adenomas. In cases of advanced adenomas, the SIR was 1.10 in patients with colonoscopic follow-up and 4.26 in those without. The 10-year cumulative probabilities of colorectal cancer were, respectively, 2.05% and 6.22%. Study investigators concluded that in routine practice, the risk of colorectal cancer after adenoma removal remains high and depends both on initial adenoma features and on colonoscopy surveillance practices. Gastroenterologists should encourage patients to comply with long-term colonoscopic surveillance.

Cottet, Vanessa, et al., Long term risk of colorectal cancer after adenoma removal: a population-based cohort study. Gut. doi:10.1136/gutjnl-2011-300295

24. Ulcerative Colitis and Colorectal Cancer in Older Patients (Jan.11/12)

While ulcerative colitis (UC) is a risk factor for colorectal cancer, the association of UC with survival after colorectal cancer has not been studied in an older population. The objective of the study was to compare the survival of colorectal cancer between persons with and without UC. All cases of colorectal cancer (CRC) in persons 67 and older between 1993 and 1999 were assessed. Investigators compared survival between individuals with UC and CRC (UC-CRC) and sporadic CRC. They identified 47,543 cases of colorectal cancer. Cases with UC-CRC tend to be diagnosed at earlier stages compared to sporadic CRC [42 vs. 37% local (TNM stage 1 and 2) and 11 vs. 17% distant spread (TNM stage 4), respectively]. Controlling for age, gender, race and stage, diagnosis of UC did not affect the 3-year survival for CRC. Colorectal cancers tend to be diagnosed at earlier stages among persons with UC, but there is no difference in 3-year survival rates for colorectal cancer among individuals with and without UC.

Shaukat, Aasma, et al., Is ulcerative colitis associated with survival among older persons with colorectal cancer in the US? A population-based case-control study. Digestive Diseases & Sciences. 2011 Nov 19. [Epub ahead of print].

25. What is Genomics? (Jan.13/12)

You've probably heard of genetic testing for cancer susceptibility, but the more recent and broader field of genomics is also having a wide-reaching impact on patient care. To start with the more familiar term, *genetics* is the study of single genes and their effects. For example, certain inherited mutations in the BRCA1 or BRCA2 genes greatly increase a woman's risk of breast and ovarian cancer. Mutations in these genes can be passed down through either the mother's or the father's side of the family. If a woman tests positive for a BRCA mutation, there are steps that she can take to reduce her cancer risk or to detect cancer at an early stage. ***Genomics*** generally refers to the study of the entire genome (all of the DNA in an organism). Genomics can consider multiple genes and how they interact with each other and the environment to affect health. Examples of genomic tests are the Oncotype DX breast and colon cancer tests. The tests evaluate the activity of several genes in a sample of tumor tissue in order to assess the likelihood of cancer recurrence. Information about recurrence risk can affect treatment decisions. Similarly, research that combines genomics with pharmacology (pharmacogenomics) is studying how genetic variation affects an individual's response to particular medications. Variability in genes involved with drug metabolism can have a substantial effect on drug response and drug side effects. Progress in this area is likely to contribute to more individualized, more effective, and less toxic drug treatments. In short, research in genomics is expanding at a rapid rate and will have a profound effect on many aspects of disease prevention, diagnosis, and treatment. Diseases such as cancer are remarkably complex; genomics provides researchers and physicians with tools to explore and address these complexities.

http://news.cancerconnect.com/what-is-genomics/

26. Myotonic Muscular Dystrophy Linked with Increased Cancer Risk (Jan.13/12)

People with myotonic muscular dystrophy may be more likely than people in the general population to develop certain types of cancer, including colon cancer. Myotonic muscular dystrophy (MMD) is the most common form of adult-onset muscular dystrophy. The condition is characterized by progressive muscle wasting and weakness. Some reports have suggested that people with MMD may have an increased risk of benign and malignant tumors. To further explore this issue, researchers conducted a study among more than 1,600 people who were diagnosed with MMD in Sweden or Denmark between 1977 and 2008. The cancer risk in the study participants was compared with the cancer risk in the general population of those countries.

- 104 MMD patients were diagnosed with cancer during follow-up. In a similar group of people from the general population, only 52 cases of cancer would be expected.
- Types of cancer that were significantly more common among the MMD patients than among the general population were endometrial cancer (cancer of the lining of the uterus), brain cancer, ovarian cancer, and **colon cancer**. Other types of cancer that may be more common among MMD patients include eye cancer, female genital cancer, thyroid cancer, and pancreatic cancer.

These results suggest that people with MMD may have an increased risk of several types of cancer. People with MMD may wish to talk with their doctor about recommended cancer screening tests and other ways to manage their cancer risk.

Gadalla SM, et al. Cancer risk among patients with myotonic muscular dystrophy.* JAMA*. 2011;306(22):2480-2486.

NUTRITION & HEALTHY LIFESTYLE

27. Prediagnosis BMI Predicts Mortality in CRC Patients (Nov. 29/11)

For patients with nonmetastatic colorectal cancer (CRC), prediagnosis, but not postdiagnosis, body mass index (BMI) is an important predictor of mortality; and patients with type 2 diabetes mellitus (T2DM) have

a higher risk of mortality, according to two new studies. In the first study, investigators examined the association of pre- and postdiagnosis BMI with all-cause and cause-specific survival in 2,303 participants in the Cancer Prevention Study-II Nutrition Cohort with nonmetastatic CRC. Compared with normal prediagnosis BMI (18.5 to 24.9 kg/m²), obese BMI (≥30 kg/m²) was significantly associated with a higher risk of mortality from all causes, CRC, and cardiovascular disease (CVD). Post-diagnosis BMI showed no correlation with mortality. In the second study, researchers investigated the association between T2DM and survival in 2,278 participants in the Cancer Prevention Study-II Nutrition Cohort with nonmetastatic CRC. Patients with CRC and T2DM had a higher risk of all-cause, CRC-specific, and CVD-specific mortality than those without T2DM. There was no variation by gender, or by durations of T2DM or insulin use. Insulin use was associated with increased risk of death from all causes and CVD, but not from CRC, compared with no T2DM. The study authors concluded: "T2DM is associated with poorer prognosis among patients with CRC".

Campbell, Peter, et al., Impact of body index on survival after colorectal cancer diagnosis: the cancer prevention study-II nutrition cohort. J of Clin Onc. Published online before print Nov. 28, 2011.

Dehal, Ahmed, et al., Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the cancer prevention study-II nutrition cohort. J of Clin Onc. Published online before print Nov. 28, 2011.

28. High Blood Sugar Increases Women's Risk for CRC (Nov. 29/11)

Scientists at Albert Einstein College of Medicine, analyzed blood samples from 4,902 postmenopausal women in the NIH Women's Health Initiative study. Both blood glucose and blood insulin levels were measured when women entered the study. After 12 years, 81 women had been diagnosed with colorectal cancer. Women who had the **highest levels of glucose** in their blood at the beginning of the study were twice as likely to have colon or rectal cancer as those with the lowest readings. Surprisingly, initial circulating insulin levels made no difference. The study author Geoffrey Kabat concluded: *The next challenge is to find the mechanism by which chronically elevated blood glucose levels may lead to colorectal cancer. It's possible that elevated glucose levels are linked to increased blood levels of growth factors and inflammatory factors that spur the growth of intestinal polyps, some of which later develop into cancer.*

Kabat, GC, et al., A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. British J of Cancer. Advance online publication. Nov. 29, 2011.

29. Exercise Cuts Colorectal Cancer Risk (Dec. 19/11)

Researchers have found people who engage in vigorous physical activity may be protected against types of colorectal cancer. They examined 870 participants who had bowel cancer and a control group of 996 who did not have the disease. Study participants were asked to answer questions about their recreational physical activity, lifestyle, diet, medication and occupation. The study found people who performed regular vigorous physical activity over their lifetime had a 40% reduced risk of cancer of the distal (lower) colon and rectum. These results suggest that vigorous activity like jogging, cycling, swimming, tennis, hockey, netball and football may be the most effective physical activities to lower the risk of bowel cancer. Of the possible mechanisms linking physical activity and colon cancer, there is evidence to suggest that obesity and vitamin D may have a great effect on distal colon cancer than proximal colon cancer. While the link between physical activity and colon cancers remains opaque, this study supports the suggestion that lifestyle factors are more strongly tied to distal colon cancer than proximal colon cancer. Another finding showed physical activity performed after the age of 51 years, may be more beneficial in reducing the risk of distal colon cancer than physical activity performed earlier in life.

Boyle, Terry, et al., Timing and intensity of recreational physical activity and the risk of subsite-specific colorectal cancer. Cancer Causes and Control. Vol. 22, No.12: pp. 1647-1658

30. Obese Patients May Have Worse Colon Cancer Outcomes (Dec.27/11)

According to the results of this study, obese patients with colon cancer are less likely to have deficient mismatch repair (**dMMR** – please see description in Item # 21 of this document) tumors and have a worse prognosis compared with normal-weight patients, independent of other tumor variables. Investigators analyzed data from 2,693 patients with stage II or III colon cancer. The associations between body mass index (BMI) and MMR status, and BMI and survival, were analyzed. The researchers found that, overall, 16% of tumors showed dMMR and 23% of patients were obese (BMI, ≥30 kg/m²). Obesity was significantly associated with lower rates of dMMR tumors, even after adjusting for tumor site, tumor stage, sex, and age. ***Obese patients with colon cancer had significantly higher recurrence rates, shorter time to recurrence, worse disease-free survival (DFS), and worse overall survival (OS) rates compared with normal-weight patients,*** even after adjusting for other variables. **Rates of dMMR were higher in obese women than in obese men** (13 versus 8%). Patients with dMMR colon cancers had significantly longer DFS and OS than patients with proficient MMR tumors. The study authors concluded: "*Colon cancers from obese patients are less likely to show dMMR, suggesting obesity-related differences in the pathogenesis of colon cancer. Although obesity was independently associated with adverse outcome, the favorable prognostic impact of dMMR was maintained among obese patients*".

Sinicrope, Frank, et al., Association of obesity with DNA mismatch repair status and clinical outcome in patients with stage II or III colon carcinoma participating in NCCTG and NSABP adjuvant chemotherapy trials. J of Clin Onc. Published online before print Dec. 27, 2011.

31. Obesity & Cancer Screening (Jan.13/12)

According to this recent study, obesity is associated with higher rates of prostate cancer screening amongst all races and ethnic differences as well as lower rates of cervical cancer screening predominantly in white women. The study examined the role of obesity in cancer screening rates for prostate, cervical as well as breast and **colorectal cancers** across race, ethnicity and gender. Numerous studies have suggested that obesity constitutes an obstacle to cancer screening, but a deeper examination also considering the role of race/ethnicity and gender in the equation has not been done before. A greater understanding of the relationship between cancer screening and obesity, race/ethnicity and gender can also help explain the association between obesity and increased cancer mortality. After tobacco, obesity is the second highest risk factor for cancer. Obesity is linked to a higher death rate for all cancers combined and also for specific cancers, such as cancer of the **colon/rectum**, prostate, breast, and cervix cancer. As it relates to colorectal cancer, the study revealed that women of higher weight tended to receive less screening for colorectal cancer (CRC), and even though the data contained no reference to differences in screening levels amongst different races, the study did demonstrate inconsistencies in the link between obesity and CRC screening in men. A direct comparison was difficult in the studies on CRC screening as these included a variety of testing options, however, overall the findings revealed that endoscopy and not fecal occult blood tests (FOBT) were more likely to be influenced by a person's weight status, particularly in women. The researchers speculate that this could be linked to endoscopy being a more invasive procedure and therefore more difficult in obese patients as compared with other screening tests. The findings demonstrated that certain cancer screenings could either be limited or accessible depending on cultural differences amongst males and females, black or white individuals and socioeconomic factors like insurance status and access to health care, which can be confounded with race/ethnicity and gender.

http://www.medicalnewstoday.com/articles/240252.php