

A have to
COLORECTAL CANCER RESEARCH
Month Ending July 16, 2010



The following colorectal cancer research update extends from June 26 – July 16, 2010 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. **Perifosine Increases Efficacy of Xeloda** (Jun. 29/10)

According to this study, colorectal cancer patients whose tumors had grown and spread after two or more other chemotherapy regimens benefitted when **perifosine** was added to Xeloda chemotherapy. Both

the time until cancer got worse and survival time improved with perifosine compared to a placebo. This held true for patients who had received 5-FU previously.

For the 35 patients whose results were analyzed:

- Median time to progression was 28 weeks for patients who received Xeloda plus perifosine and 11 weeks for those who received Xeloda with a placebo.
- Overall survival time was 18 months with perifosine and 11 months with Xeloda alone.
- Tumors shrank (*complete or partial response*) for 4 patients in the perifosine arm compared to 1 patient getting Xeloda and a placebo.
- 55% of patients on perifosine had stable disease that lasted more than 12 weeks compared to 33% for Xeloda alone.
- Overall 3 out of 4 (75%) had either a response to the combination of perifosine and Xeloda or stable disease, compared to 40% of those who got a placebo with Xeloda.
- The patient with a complete response lived 3 years before cancer got worse. The three patients with partial responses lived 21, 19, and 11 months before progression.

For 25 patients who had taken 5-FU previously:

- There was 1 partial response that lasted 19 months in the perifosine arm.
- Median overall survival time on perifosine was 15.1 months compared to 6.6 months on Xeloda only.
- Median time to progression was 18 weeks with perifosine compared to 10 weeks on Xeloda with a placebo.

Serious side effects seen more often with the perifosine-Xeloda combination were hand-foot syndrome and anemia. Less serious (grade 1 and 2) side effects that were seen more often in the combination treatment were diarrhea, fatigue, nausea, muscle pain, mouth sores, lack of appetite, hand-foot syndrome and anemia. However, patients in the combination arm received treatment for a longer period of time. Patients in the trial had cancer get worse (*progress*) on at least 2 previous treatments. 90% had been on FOLFIRI, 75 to 80% on FOLFOX. 3 out of 4 had received Avastin and about half Erbitux or Vectibix. Researchers concluded that the perifosine-xeloda is a well-tolerated regimen that has promising activity over xeloda alone as second or third line therapy for patients with metastatic colorectal cancer and that the improvement is consistent for those patients with 5FU refractory disease. A phase III trial is forthcoming.

Richards, D.A., et al., Final results of a randomized phase II study of perifosine in combination with capecitabine versus placebo plus capecitabine in patients with second or third line metastatic colorectal cancer. J Clin Oncology. 28:15s.2010. (ASCO, abstract 3531)

2. The Connection Between DNA Mismatch Repair and 5FU Therapy (Jun. 29/10)

The following shall serve as a prelude in helping to understand the results of the next piece of research:

*There are 2 kinds of colon cancer genetics: There is the familial polyposis genetics, rarely inherited but commonly acquired. Eighty percent of all colon cancer follows those genetics. In essence, all of those patients are microsatellite stable or proficient in mismatch repair (normal). **Mismatch repair** refers to those mistakes that result in DNA during cell division; when they are caught early and fixed by the cell, we call this **proficient or stable mismatch repair or pMMR or sMMR**. That leaves 20%, and these 20% share the genetics of the Lynch syndrome, HNPCC (hereditary nonpolyposis colorectal cancer), which has mismatch repair deficiencies or is deficient in mismatch repair, wherein the mistakes are not caught and corrected, which leads to MSI. Hence, "**MSI high**" is **mismatch repair deficient**. Now, only about 20% of the patients are going to be MSI high, and about 6% of all colon cancer will have inherited MSI high. The broken gene, MSI (deficient mismatch repair), is actually a good prognostic sign, particularly **in stage II colon cancer**, and it appears as though chemotherapy may be harmful or at least not beneficial in that subgroup. Therefore, checking MSI status in stage II patients is strongly recommended because it is important to discover if they are MSI high, in which case they would not be administered chemotherapy. In conclusion, patients are either MSS (stable) or MSI high, meaning that they have deficient mismatch repair. And most of the patients will be MSS, and the MSI high group should not be administered chemo.*

Microsatellite Instability:

The normal length of microsatellites in an individual's cells is set at birth, although lengths vary from one person to another. However, during the many divisions cells undergo in a person's lifetime, mistakes can be made duplicating DNA which don't get repaired, so microsatellites change in length in some tissues (as depicted in the diagram above). The presence of abnormally short or long microsatellites indicates that genes that should be repairing DNA are mutated and aren't doing their job. Mutations in DNA repair genes can lead to a particular form of colorectal cancer linked to microsatellite instability. About 1 in 6 or 7 (15%) colorectal cancers are microsatellite unstable. Some people are born with mutations in DNA repair genes, as in Lynch syndrome. Others acquire mutations during their lives. Here are the classifications of Microsatellite Instability:

Microsatellite Instability High Tumours: Contain changes in 2 or more regions of the DNA (genetic material) of the tumour

Microsatellite Instability Low Tumours: Contain changes in one region of the DNA of the tumour.

Microsatellite Instability Stable Tumours: Contain no changes in the DNA of the tumour]

According to this study, some colon cancer patients don't benefit from treatment with 5-FU based chemotherapy and may even have worse outcomes than if they had no chemo at all. Of every 100 people with colon cancer, approximately 15 will have cancers that arise when mistakes in DNA during cell division are not caught and fixed. Scientists call this **defective mismatch repair or dMMR**. More often, colon cancer occurs when mutations in chromosomes accumulate but DNA repair pathways remain intact and mismatch repair is *proficient* (pMMR). This is true for approximately 85% of colon cancer. Both prognosis and the potential benefit from FU-based chemotherapy appear to be very different for these two types of colon cancer. Knowing mismatch repair status of colon tumors can help patients and their doctors make better treatment decisions. Patients with defective mismatch repair have better disease-free and overall survival and don't seem to benefit from 5-FU at either stage II or stage III. Stage II patients with dMMR have significantly poorer overall survival if they get chemo after surgery. Please note that these *results come from studies of 5-FU plus levamisole or 5-FU plus leucovorin. They don't include any information from the current standard treatments of FOLFOX or FLOX which contain oxaliplatin in addition to 5-FU and leucovorin.* Defective mismatch repair is uncovered when either tumors have *microsatellite instability (MSI)* or immunohistochemical tests can't find the proteins that are expressed by genes that control mismatch repair — MLH1, MSH2, MSH6, and PMS2. Measuring either MSI or lack of MLH1 or MSH2 expression gives similar results in deciding whether a tumor is mismatch defective or proficient. Almost all defective mismatch repair tumors are located in the right side of the colon. They are poorly differentiated, often have lots of mucus, and tend to be infiltrated with immune-system cells (lymphocytes). Some scientists speculate that it is this improved immune-response that gives them their survival advantage. The results of this study are as follows:

Mismatch Repair Status as a Prognostic Marker

- Patients with **defective mismatch repair (dMMR) who didn't get 5-FU** had significantly **better disease-free and overall survival** than patients with proficient mismatch repair (pMMR).
- When patients received **chemotherapy**, mismatch repair status had **no impact on survival**.

Mismatch Repair Status as a Predictive Marker for FU- based chemotherapy

- There was **no benefit** of FU-based chemotherapy for **either stage II or stage III colon cancer patients with defective mismatch repair**.
- There was **no benefit** of FU chemo for **stage II patients with proficient mismatch repair**.
- **Stage III patients with pMMR did benefit** from chemotherapy with 5-FU.
- **Stage II patients with dMMR had worse overall survival** when they received 5-FU than when they had surgery alone.

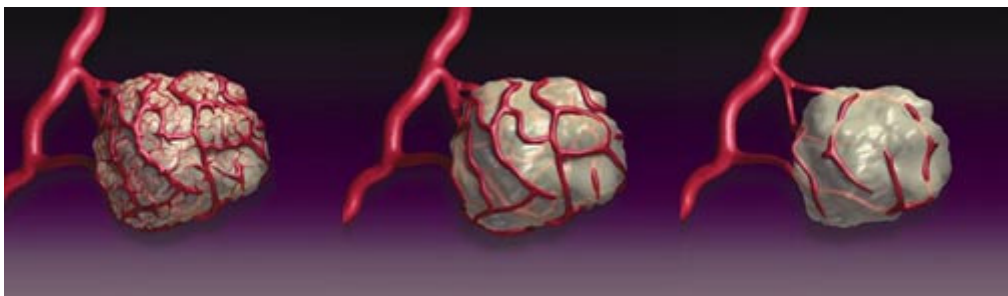
Investigators concluded that dMMR colon cancers have a favorable stage adjusted prognosis compared with the majority of colon cancers; and patients with dMMR colon cancers do not benefit from FU based adjuvant therapy.

Sargent, Daniel, et al., Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil based adjuvant therapy in colon cancer. J of Clini Oncology, Vol. 28, No. 20 (July 10), 2010: pp. 3219-3226

3. Maintenance Avastin Monotherapy Equals Combination Therapy for Metastatic Colorectal Cancer (Jul. 5/10)

According to this study, maintenance therapy with Avastin or bevacizumab may be an appropriate treatment option following capecitabine and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer. The aim of the study was to evaluate the efficacy and tolerability of 6 cycles of oxaliplatin/bevacizumab followed by maintenance therapy with oxaliplatin/bevacizumab **or** bevacizumab alone. Patients aged 18 years and older with confirmed metastatic colorectal cancer received first-line treatment with capecitabine and oxaliplatin plus bevacizumab every 3 weeks for 6 cycles. Patients were then randomized to continue with this treatment or to receive maintenance therapy with bevacizumab alone. The primary endpoint of progression-free survival (PFS) was not significant for patients who continued on the combination maintenance therapy versus patients who received bevacizumab monotherapy (10.4 vs 9.7 months). The same was seen for the secondary endpoints of overall survival (23.4 vs 21.7 months) and objective response rate (46% vs 49%).

Aranda, Enrique, et al., Phase iii study of first line xelox plus bevacizumab for 6 cycles followed by xelox plus bev or single agent bev as maintenance therapy in patients with metastatic colorectal cancer: the MACRO trial. Abstract 0-0021: presented at ESMO-GI 2010.



Avastin's effects on colorectal tumours include the following:

- Reducing the tumor's blood supply by potentially causing existing small blood vessels in the tumor to die.
- Preventing the development of new blood vessels in the tumor.
- Facilitating the delivery of chemotherapy to the tumor cells by potentially making mature tumor vessels, which tend to be leaky, behave more like normal vessels.

Source: <http://www.gene.com/gene/products/information/oncology/avastin/vegf-angiogenesis-cancer.html>

4. Addition of Sunitinib to Folfox or Folfiri Adds No Survival Benefit (Jul. 5/10)

First-line treatments of sunitinib combined with either FOLFOX6 (5-fluorouracil, leucovorin, oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, irinotecan) show no significant survival or response benefits over bevacizumab plus FOLFOX6 or FOLFIRI alone in patients with metastatic colorectal cancer (mCRC). The findings are based on 2 studies presented on July 3 at the European Society for Medical Oncology's 12th World Congress on Gastrointestinal Cancer (ESMO-GI). The first study randomized 191 patients to FOLFOX6 plus either bevacizumab or oral sunitinib.. The second study randomized 768 patients to FOLFIRI, plus either placebo or oral sunitinib. In both studies, the primary endpoint was increased which was progression-free survival (PFS). Progression-free survival was 9.1 months in the FOLFOX6 plus sunitinib arm and 11.2 months in the FOLFOX6 plus bevacizumab arm; and 7.8 months in the FOLFIRI plus sunitinib arm versus 8.4 months in the FOLFIRI-alone arm. Similarly, there were no significant differences in the objective tumour response rates for FOLFOX6 plus sunitinib (36%), FOLFOX6 plus bevacizumab (36%), FOLFIRI plus sunitinib (32%) and FOLFIRI alone (34%).

Hecht, et al., Sunitinib Plus 5FU, leucovorin and oxaliplatin (mFolfox6) vs. bevacizumab plus folfox6 in first line metastatic colorectal cancer – interim results of a randomized phase IIb study. Abstract 0-0014

Carrato, Alfredo, et al., Final results from a randomized, double blind, phase III study of sunitinib plus folfiri vs. placebo plus folfiri in first line treatment of patients with metastatic colorectal cancer. Abstract 0-0026

5. Adjuvant Chemo in Rectal Cancer Prevents Local Recurrence Rather Than Distant Mets (Jul. 5/10)

According to the results of this study, preoperative chemoradiotherapy followed by adjuvant chemotherapy reduced the risk for local recurrence, but not of distant metastases, in patients with locally advanced rectal cancer. Preoperative radiotherapy (RT) reduces the size of the involved area, thereby facilitating surgical resection. Normal tissue tolerance limits the dose of preoperative RT. Intraoperative radiotherapy (IORT) has been used to deliver a radiation boost to a defined volume while permitting shielding or removal of dose-sensitive structures. Local recurrence developed in 12% and the risk factors associated with local recurrence included no down staging, lymph node positivity, margin involvement and no adjuvant chemo. The local recurrence rate was 5.5% in patients who received adjuvant chemo and 12% in those who did not. The rate of distant metastases at 5 years was 29.2% and the risk factors associated with a higher risk of distant metastases were male gender, preoperative T4 disease, no down staging, lymph node positivity and margin involvement. The use of adjuvant therapy did not affect the rate of distant metastases. Investigators concluded that the use of preoperative chemoradiotherapy followed by adjuvant therapy reduced the risk of local recurrence, but not of distant metastases, in patients with locally advanced rectal cancer.

Kusters, M. et al., Results of European pooled analysis of IORT-Containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol. 2010 Jun.1; 21(6): pp. 1270-1284

6. Adding Imprime PGG to Erbitux Doubles Response in CRC Patients (Jul. 6/10)

The combination of Biothera's experimental drug Imprime PGG and Erbitux (cetuximab) doubled the overall response rate and the time to progression of second- and third-line metastatic colorectal cancer patients treated with Erbitux monotherapy. The Phase Ib/IIa study is evaluating the safety and efficacy of Imprime PGG plus irinotecan and cetuximab (Arm #1) or Imprime PGG plus cetuximab alone (Arm #2) for second- and third-line colorectal cancer patients who have been identified to be kras mutant. Results from study Arm #2 were the subject of new data released at ESMO. Arm #1 data was released at the American Society of Clinical Oncology (ASCO) annual meeting in 2009. Arm #2 of the study included 22

patients dosed with 2 mg/kg, 4 mg/kg or 6 mg/kg of Imprime PGG in combination with standard doses of cetuximab. Imprime PGG was safe and well tolerated. Imprime PGG is a novel immunotherapy that works synergistically with anti-tumor monoclonal antibodies to activate a large population of the body's immune cells (neutrophils) to kill cancer cells. Imprime PGG is currently in multiple Phase II clinical trials for lung and colorectal cancer. While some drugs trigger a broad innate immune response, Imprime PGG activates immune cells without inducing systemic pro-inflammatory cytokines that are attributed to adverse reactions. Investigators concluded that data from both arms of this trial strongly support the extensive preclinical evidence that Imprime PGG engages the innate immune system in a way that it enables it to identify and kill erbitux-targeted cancer cells.

<http://finance.yahoo.com/news/Combination-of-Imprime-PGG-bw-3317057662.html?x=0&.v=1>

7. **NKTR-102 Demonstrates Superior Activity to Irinotecan** (Jul. 6/10)

According to the results of this study, NKTR-102 appeared to exhibit superior activity compared to irinotecan as part of either a monotherapy or combination regimen in tumor models of gastrointestinal cancers. NKTR-102 targets tumor tissue through the enhanced permeation and retention (EPR) effect. Data presented at the ESMO show that NKTR-102 achieves greater and more sustained concentration of the active drug in the tumor, leading to superior activity of NKTR-102 in models of gastrointestinal cancers. The preclinical results demonstrate the potential for NKTR-102 to be developed as both a single agent and in combination with 5-FU to treat patients with metastatic colorectal cancer, and also support the comprehensive development program for NKTR-102 that includes colorectal, breast and ovarian cancers.

Activity of NKTR-102 in nonclinical models of gastrointestinal cancers" (Abstract P-0025) at the ESMO Conference: 12th World Congress on Gastrointestinal Cancer in Barcelona, Spain on July 3-5, 2010.

8. **Afinitor Combined with Avastin is Proving Helpful in the Treatment of Advanced Colorectal Cancer** (Jul. 6/10)

Some colorectal cancer patients whose tumors had gotten worse on all standard treatments benefited from a combination of Afinitor (everolimus) and Avastin (bevacizumab) during a small trial reported at the 2010 ASCO Annual meeting in Chicago. While no tumors got smaller on the treatment, approximately half of patients in the Phase II trial had their cancer remain stable for six months or more. Three patients have had stable disease for more than a year. Seven out of ten patients in the trial had at least one serious side effect. The most common was hypertension, but there were several bowel abscesses or fistulas and one case of bowel perforation. There was one death due to treatment infection. For the 50 patients who were enrolled in the trial:

- Median progression-free survival time was 2.28 months.
- Median overall survival time was 7.87 months.
- 46% of patients had disease control that lasted a median of 6.1 months
- No complete or partial responses
- 8 had a minor response lasting median 4.1 months
- 15 had stable disease lasting median 6.7 months

Afinitor is currently approved by the FDA in the U.S. for the treatment of advanced renal cell cancer. It works by inhibiting a protein within the cancer cell called mTOR. Investigators concluded that bevacizumab plus everolimus has promising activity in refractory metastatic colorectal cancer (even in patients who have progressed on a bevacizumab-based regimen) with a disease control rate of 46%, suggesting bevacizumab plus everolimus may overcome resistance to bevacizumab.

Altomare, I, et al., Phase II trial of bevacizumab plus everolimus for refractory metastatic colorectal cancer. J of Clin Onc. 28: 15s, 2010, Abstract #3535, ASCO 2010.

9. **Results of Avastin-Treated Patients** (Jul.6/10)

According to the results of this study, the use of bevacizumab beyond disease progression (BBP) shows low rates of bevacizumab-associated adverse events (AEs) and provides significant survival beyond first progressive disease (SBP) in patients with metastatic colorectal cancer. Investigators evaluated the association between early exposure to BBP and SBP. According to researchers, and also supported by the earlier BRiTE study, "These results support the hypothesis that sustained VEGF [vascular endothelial growth factor] suppression improves clinical outcomes in patients with metastatic colorectal cancer."

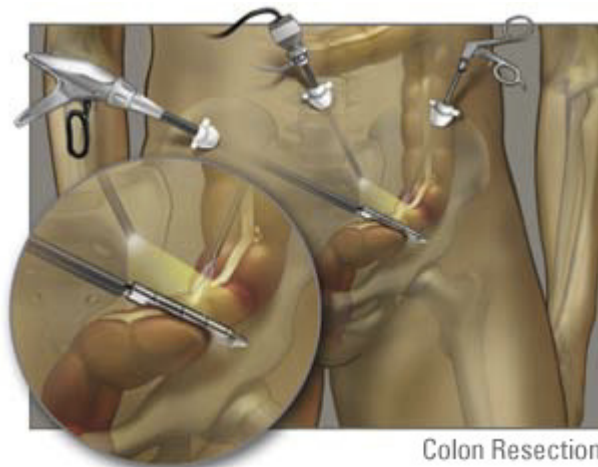
Cohn, Allen, et al., Clinical Outcomes in Bevacizumab-treated patients with metastatic colorectal cancer: results from ARIES observational cohort study and confirmation of BRiTE data on Bevacizumab beyond progression. Abstract O-0002. ESMO GI.

SURGICAL THERAPIES

10. **Open vs. Laparoscopic Surgery For Mid or Low Rectal Cancer** (June 28/10)

This study sought to compare open surgery with laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy. Patients were randomized 1:1 to receive either open surgery or laparoscopic surgery, grouped according to sex and preoperative chemotherapy regimen. The laparoscopic surgery group showed earlier recovery of bowel function than the open surgery group. The total amount of morphine used was less in the laparoscopic group than in the open group. 3 months after proctectomy or ileostomy takedown, the laparoscopic group showed better physical functioning score than the open group, less fatigue, and fewer defecation problems. Investigators concluded that laparoscopic surgery after preoperative chemoradiotherapy for mid or low rectal cancer is safe and has short term benefits compared with open surgery; the quality of oncological resection was equivalent.

Laparoscopic Colorectal Surgery



In selected patients, laparoscopic surgery is used to remove parts or in some cases the entire colon through small incisions with proven benefits compared with open surgery.

Source: http://tricitycolorectalsurgery.com/laparoscopicminimally_invasive_surgery

Kang, Sung-Bum, et al., Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short term outcomes of an open label randomized controlled trial. The Lancet Onc; Vol 11, Issue 7: pp. 637-645

11. Repeated Resection for Recurrent Pulmonary Mets (Jun. 29/10)

According to the results of this study, in the management of recurrent pulmonary metastases from colorectal cancer, repeated **metastasectomy** (surgery for metastatic disease) followed by chemotherapy improved overall long-term survival. Optimal treatment strategies are needed for patients with recurrent pulmonary metastases following initial surgical resection for metastases from colorectal cancer. Factors such as the interval between initial metastasectomy and repeat resection, the multiplicity of lesions, and the total number of metastectomies carried out could affect outcomes. In order to establish treatment standards for recurrent pulmonary metastases, South Korean researchers evaluated survival outcomes for patients undergoing repeated metastasectomy as related to these factors. The primary outcomes were overall survival (OS) and 5-year disease-free survival (DFS) following repeat metastectomies. Among the 48 patients who underwent a second metastasectomy, OS was 79.3%. Among the 10 patients who underwent a third metastasectomy, OS was 77.8%. The median DFS and 5-year DFS for the patients who underwent a second metastasectomy were 42.8 months and 48.7%, respectively. Of all the potential prognostic factors, the only significant risk factor for patients' survival was a finding of abnormally elevated preoperative CEA level. The findings from this study indicated that, in the management of recurrent pulmonary metastases from colorectal cancer, early detection of recurrence and use of repeated metastasectomy (lung tissue-saving resections), combined with preoperative and postoperative chemotherapy, can improve treatment outcomes.

Park, JS, et al., Outcomes After Repeated Resection for Recurrent Pulmonary Metastases From Colorectal Cancer. Ann Oncol. 2010 June. Epub ahead of print. 21(6): 1285-1289

12. Laparoscopic vs. Open Surgery for Rectal Cancer (Jul. 12/10)

There are few reports that show that laparoscopic rectal surgery for rectal cancer has similar oncological results based on short-term benefits. The purpose of this study was to analyze institutional short- and long-term results in laparoscopic rectal surgery and to compare these results with that reported in the literature. The records of 121 patients who underwent sphincter-saving procedure for rectal cancer were reviewed. The variables analyzed included possible

- factors causing morbidity,
- anastomotic leak, and
- recurrence rate in the laparoscopic and open techniques.

Laparoscopic sphincter-saving total mesorectal excision or partial mesorectal excision was performed in 97 patients (group 1). Twenty-four patients had open procedure (group 2). The conversion rate from laparoscopic to open technique was 10.3%. There was no statistical difference in terms of postoperative morbidity and anastomotic leak between the two groups. Investigators concluded that laparoscopic sphincter-saving rectal resection for rectal cancer shows good long-term results. However, it has no advantage in terms of short-term benefits compared with the open procedure. Further studies are needed to validate the effect of down staging on anastomotic leaks.

Lam, HD., et al., Laparoscopic versus open techniques in rectal cancer surgery: a retrospective analysis of 121 sphincter-saving procedures in a single institution. Surgical Endoscopy. DOI: 10.1007/s00464-010-1191-y

RADIATION / INTERVENTIONAL RADIOLOGY

13. Radioembolization with 5FU Helps Colorectal Liver Mets (Jul.8/10)

Radioembolization plus the chemotherapy agent fluorouracil (5FU) appears to slow cancer progression for colorectal cancer patients whose disease has progressed following prior treatment with chemotherapy and have metastases limited to the liver. The primary cause of death related to colorectal cancer is cancer spread to the liver, referred to as liver metastasis. The surgical removal of liver metastasis appears to provide optimal outcomes for patients with this stage of disease. However, patients are often not able to have this type of surgery. Reasons a patient may not be eligible for surgical removal of liver metastasis include:

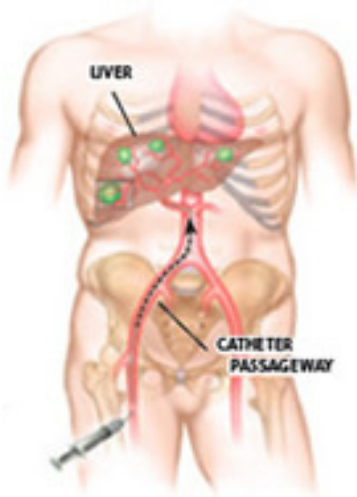
- the extent of cancer spread within the liver;
- the size of cancerous tumors within the liver;
- placement of the cancer within the liver;
- a patient's overall health.

Patients with inoperable liver metastasis may be treated with chemotherapy, radiofrequency ablation (a procedure in which radio waves are directed into the tumor(s) with a probe), or radiation therapy. With a goal of improving the duration of survival for these patients, researchers continue to evaluate novel ways to treat inoperable liver metastasis. **Radioembolization** is another strategy to optimize the delivery of radiation to liver metastases while sparing healthy tissue. This strategy utilizes radioactive **microspheres** (small spheres containing radioactive material – *please see image and description below*). The small spheres are injected into the vasculature (blood vessels) of the liver, where they tend to get lodged in the vasculature responsible for providing blood and nourishment to the cancer cells. While lodged in place, the radioactive substance spontaneously emits radiation to the surrounding cancerous area while minimizing radiation exposure to the healthy portions of the liver. Results from a previous small study indicated that radioembolization with concomitant chemotherapy (oxaliplatin, fluorouracil, and leucovorin) was active in colorectal cancer patients with inoperable liver metastases who had no prior treatment; median time to cancer progression within the liver in this study was over one year. This current study—a large prospective, multicenter, randomized Phase III trial—was designed to evaluate the safety and efficacy of radioembolization combined with the chemotherapy agent fluorouracil in heavily pretreated colorectal cancer patients. All 44 patients in this study had metastatic colorectal cancer with inoperable metastases limited to the liver and had disease progression following standard chemotherapy including the agents fluorouracil, oxaliplatin, and irinotecan. Patients were randomized to receive treatment with fluorouracil alone or radioembolization plus fluorouracil. At a median follow-up of 24.8 months, radioembolization plus fluorouracil **significantly improved the median time to tumor progression** and the time to liver progression (see Table 1 below). In addition, treatment with the radioembolization plus fluorouracil was well tolerated with only one patient experiencing significant toxicity compared with six patients in the fluorouracil arm.

Table 1: Time to liver progression, time to tumor progression, and median overall survival for patients receiving fluorouracil alone compared with radioembolization plus fluorouracil.

	Fluorouracil Alone (n=23)	Radioembolization plus fluorouracil (n=21)	P value
Median time to liver progression (months)	2.1	5.5	.003
Median time to tumor progression (months)	2.1	4.5	.03
Median overall survival (months)	7.3	10.0	.80

The researchers concluded that radioembolization combined with fluorouracil may benefit metastatic colorectal cancer patients with liver-limited disease who have progressed following prior chemotherapy.



SIR-Spheres microspheres are an innovative means of treating liver cancer or liver mets. In cases where it is not possible to surgically remove the liver tumors, SIR-Spheres microspheres can be used to deliver targeted, internal radiation therapy directly to the tumor.

This technique uses millions of tiny polymer beads or microspheres which contain a radioactive element called yttrium-90. SIR-Spheres microspheres are very small, approximately 32 microns in size, and are about one-third the diameter of a strand of hair. SIRT is usually administered as an outpatient procedure by a specially trained physician known as an interventional radiologist. A small catheter is guided into the liver and the SIR-Spheres microspheres are infused through the catheter.



The microspheres with the radioactive yttrium-90 are carried by the bloodstream directly to the tumors in the liver where they preferentially lodge in the small vessels feeding the tumor and deliver their dose of radiation. Unlike conventional external beam radiation, which can only be applied to limited areas of the body, SIR-Spheres microspheres selectively irradiate the tumors and therefore have the ability to deliver more potent doses of radiation directly to the cancer cells over a longer period of time.

Source: <http://www.iconradiology.com/oncology-radiology-liver-tumor-portland-oregon.htm>

Hendlisz A, et al. Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy. *Journal of Clinical Oncology* [early online publication]. June, 21 2010.

SCREENING

14. Colonoscopy Should Target High Risk Patients (Jul. 1/10)

According to this study, surveillance colonoscopy should target individuals with high risk for colorectal cancer who are most likely to benefit. The study examined the cost-effectiveness of various surveillance strategies and concluded that overuse of colonoscopy as a surveillance tool aimed at decreasing the burden of colorectal cancer can be excessively costly, and even harmful. Guidelines already state that low-risk patients should undergo surveillance every 5 to 10 years, which is in keeping with the results. However, 10-year intervals are not frequently used in clinical practice. The study suggests that, for low-risk patients, a 10-year interval is probably reasonable, and that a 3-year interval is too aggressive.

Saini, SD, et al., *Surveillance colonoscopy is cost-effective for patients with adenomas who are at high risk of colorectal cancer. Gastro. 2010 Jun; 138(7): pp. 2292-2299.*

15. Hot Weather May Affect Screening Test FIT (Jul. 7/10)

According to this study, an immunochemical test used to detect signs of colorectal cancer is less accurate when done in the summer than in cooler times of the year. Although the particular brand of test used in the study -- the OC-Hemodia test -- is not used in the Canada or the United States, the findings are of interest researchers because immunochemical fecal occult blood tests are gradually replacing the conventional stool test for colorectal cancer. Cancers of the colon or rectum generally have a good prognosis when caught early, and the most common, non-invasive way to detect it is a procedure known as the fecal occult blood test, or FOBT, which looks for blood hidden in the stool. In Italy the conventional procedure is an immunochemical fecal occult blood test. In this study, researchers noted that blood samples, if present, appeared less stable at higher temperatures -- something that may have implications for similar tests. However, the study has important limitations. The Italian researchers "looked at only one test, [and] there are a number of these tests on the market." And most immunochemical fecal occult blood tests used require several samples, as opposed to the single sample of the OC-Hemodia test. Therefore, having several samples tested may lessen the problem of inaccurate results, if they exist. In the United States and in Canada, the conventional tool for non-invasive colorectal cancer screening has traditionally been the guaiac fecal occult blood test, which involves testing stool

smears for hidden blood. However, many immunochemical fecal blood tests have been approved for marketing. Further testing is recommended.

<http://www.medicinenet.com/script/main/art.asp?articlekey=117846>

16. **Over The Counter Laxative More Effective Than Prescription Drug for Constipation** (Jul. 7/10)

According to this study, a treatment for chronic constipation that is now available over-the-counter was more effective than a prescription drug. Both polyethylene glycol, which is marketed as Miralax®, and prescription lactulose, sold under a number of brand names including Cholac Syrup®, Kristalose®, and Enulose®, work by drawing water into the colon and softening stools making them easier to pass. The two *osmotic laxatives* can help patients whose intestinal activity is slow because of illness or medicines. Cancer patients who take opiate pain relievers often have problems with this kind of constipation. Researchers found that polyethylene glycol (PEG) was better than lactulose in

- number of stools per week.
- form of stool.
- need for additional products to manage constipation.
- for children, but not adults, amount of abdominal pain.

The authors concluded that Polyethylene Glycol should be used in preference to Lactulose in the treatment of Chronic Constipation.

Lee-Robichaud et al., Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database of Systematic Reviews 2010, Issue 7.

PSYCHO-SOCIAL

17. **Reducing Stress for Cancer Caregivers** (Jun. 23/10)

If you are caring for a loved one with cancer, you may be at risk of developing stress and anxiety. This can lead to a host of symptoms, from sleeplessness to poor health. Taking control of the situation by caring for yourself is vital. It will improve your own health and your ability to care for your loved one with patience and kindness. About.com has some suggestions that may help appearing below:

1. **Eat Right**

If you're stressed because of demands on your time, it's important to make smart food choices. You may be tempted to raid the vending machine or grab a bag of chips when your stomach rumbles. Unfortunately, these foods can worsen your stress level. These simple carbohydrates can cause levels of insulin and other hormones in your body to fluctuate widely. This can lead to the post-meal crash, crankiness, and a desire to reach for more junk food later. Instead, try easy, healthy foods, such as instant plain oatmeal, yogurt, frozen fruit and veggies, an apple and peanut butter, or low-sodium bean soup.

2. **Sleep Right**

For many people, stress can lead to insomnia, or difficulty falling and staying asleep. But getting good sleep is an important part of feeling your best. Sleep also helps the body cope with stress better. Lack of sleep actually can heighten stress. A few simple tips, from darkening your bedroom completely to creating a bedtime ritual to trying patterned breathing, will help you get your Z's.

3. **Exercise**

Even if you've never exercised, a few minutes of movement per day can significantly lower stress levels. In fact, one of the best things you can do is something most of us have been doing for our whole lives: walking. Try a 10-minute walk at lunch and first thing after work. If you're at home, get a breath of fresh air mid-day. Don't let rain stop you either. As long as it's not thundering or lightning, an umbrella is all you need. And if you're a regular gym rat, but can't get there now due to time demands, don't fall prey to "all or nothing" thinking. Anything, even a quick walk, is better than nothing.

4. **Take "Me" Time**

You may feel selfish taking time for yourself during a loved one's health crisis, but you shouldn't. If you give and give and give, but never take a minute of "me" time, you'll quickly feel resentful and burnt out on caregiving. Try to set aside just 5 to 10 minutes a day to read a few pages of your favorite magazine or book, call a friend, do some deep breathing, or do whatever it is that helps you feel better and relax.

5. Accept Help

It's hard to accept help. This is especially true if you are a "natural caregiver." It may feel like you're failing when you accept help, but it's just the opposite. Getting help will make it more likely that both you and your loved one with cancer will get what you need.

The best way to get the help you need is to be specific. If someone offers to help, give them a specific task. For example, "If you could come over at 4pm on Tuesday to keep Jane company while I run the kids to ballet and soccer, it would be a huge help." Or, "I'd love some help with the yard work. Can you rake on Saturday at 11am?"

6. Tap Into Resources

Many cancer centers have support groups for family caregivers. These groups can be an invaluable source of support and ideas for coping. Ask the nurse if the cancer treatment facility has caregiver, family, or spouse support groups. If you can't locate a caregiver support group through your local cancer treatment program, try searching online for the phrase "caregiver support groups" (no quotes) plus the name of your state or city. You can find several options this way. Even an online support group can help you cope and give you a place to talk to people going through situations similar to yours.

7. Get Professional Help

If you are caring for someone with incurable cancer or who has other serious medical conditions, you may need a visiting nurse or other in home care. Many people make the mistake of waiting until the "last minute," when a loved one is very sick, before seeking professional help. This makes your life tougher than it needs to be and may lead to more disability and suffering for your loved one.

<http://coloncancer.about.com/od/additionalresources/ht/HowToCopeWithCaregiverStress.htm>

18. Top 5 Caregiver Stress Symptoms (Jun. 23/10)

About.com has also identified the top 5 caregiver stress symptoms to aid caregivers during their time with their afflicted loved ones. Identification of the symptoms is the first step to helping address and resolve those symptoms.

Caregiver stress symptoms can negatively affect your physical and mental health. Even worse is when caregiver stress symptoms lead to caregiver burnout. If you are taking care of a loved one with cancer, recognizing the top 5 caregiver stress symptoms is important. Knowing these symptoms will help you get the support you need to avoid full-blown caregiver burnout.

1. **Stress Symptom #1 – Sleeplessness:** When you add the responsibility of caring for a loved one to your regular responsibilities, it can lead to sleeplessness. Insomnia plagues millions of Americans who *aren't* caring for someone with cancer, so it's no surprise that it can affect those who are. You may toss and turn, lying awake while thinking, "How will I get it all done? Between work, the errands, the kids, and now getting John to appointments, how will I fit it in?" The worst part of sleeplessness is that it can contribute to exhaustion, making it even harder to tackle your to-do list.
2. **Stress Symptom #2 - Irritability and Trouble Concentrating:** When stressed, it's easy to become irritable and have trouble concentrating. And if you're not sleeping well, your fuse will be even shorter. You may find yourself snapping at your loved ones when they ask a question or want your attention. If you feel more irritable than normal or you can't concentrate at work or home, you may be headed for caregiver burnout.
3. **Stress Symptom #3 - Anxiety and Depression:** When you have a lot on your plate, it's easy to become anxious or depressed. You may be anxious that you'll fall short of meeting your loved one's needs. You may feel depressed that life will never be pleasurable for you again. And your anxiety can even have a physical cause. For example, if you aren't sleeping well, your body will produce more stress hormones, such as cortisol. This can heighten your anxiety even further.
4. **Stress Symptom #4 - Denial and Anger:** When faced with a loved one's serious illness, it's easy to bury your head in the sand. You may be thinking, "She'll be better in no time. The treatment will be a cinch." It's also easy to find this denial leading to anger. "Why us? Why cancer? It's not fair," are common responses to a cancer diagnosis. This is completely normal, but if denial and anger linger and prevent you from addressing the situation constructively, this can be a sign of caregiver stress. For example, if you're in denial, you may not take the needed steps to take care of your loved one. You may need to line up friends and other family members to help with appointments and chores. Denial can make this seem unnecessary.
5. **Stress Symptom #5 - Poor Health:** It's not news that your physical and mental health can suffer due to the stress of caring for someone with cancer. If you're stressed, you may not be sleeping well. You may stop exercising. Many caregivers have guilt over taking time for themselves. Even something as simple as a walk can bring on guilty feelings about all of the other things you should be doing. You may be eating poorly too. If you feel fatigued, you have lots of aches and pains, chronic headaches,

or any other health issues cropping up, your caregiver stress may be pushing you toward caregiver burnout.

<http://coloncancer.about.com/od/additionalresources/f/Caregiver-Stress-FAQ.htm>

OTHER

19. Tardy Diagnosis Does Not Affect Survival of Metastatic Colorectal Cancer Patients (Jun. 29/10)

Diagnosing colorectal cancer (CRC) at an early stage improves survival. To what extent any delay affects outcome once patients are symptomatic is still unclear. Our objectives were to evaluate the association between diagnostic delay and survival in symptomatic patients with early stage CRC and late stage CRC. In total, 272 patients were available for analysis. Early stage CRC was present in 136 patients while 136 patients had late stage CRC. The mean total diagnostic delay (SE) was 31 (1.5) weeks in all CRC patients. No significant difference was observed in the mean total diagnostic delay in early versus late stage CRC. In early stage CRC, no difference in survival was observed between patients with total diagnostic delay shorter and longer than the median. In late stage CRC, patients with a diagnostic delay shorter than the median had a shorter survival than patients with a diagnostic delay longer than the median. In symptomatic CRC patients, a longer diagnostic and therapeutic delay in routine clinical practice was not associated with an adverse effect on survival. The time to CRC diagnosis and initiation of treatment did not differ between early stage and late stage colorectal cancer.

Terhaar, Jochim, et al., Does delay in diagnosing colorectal cancer in symptomatic patients affect tumour stage and survival? A population-based observational study. BMC Cancer 2010, 10:332 doi:10.1186/1471-2407-10-332

20. Research Validates the Potential For a Cure of Metastatic Colorectal Cancer (Jun. 29/10)

Metastatic refers to cancer that has spread beyond the original tumor to other areas of the body. For nearly all of the 20th century, metastatic colon cancer was considered incurable. But a just-published review of the research on metastatic colon cancer discusses how changes in treatment have moved us closer to a day when even metastatic colon cancer will be curable. In the review, the authors provide details of how cancer treatment advances of the past few years have made long-term survival after metastatic colon cancer a reality for a small number of people. Unfortunately, a complete cure of metastatic colon cancer is not possible for many, but the median survival has increased from 5 months to 2 years. This points to a time when advanced colon cancer may become a "chronic disease." It may not be technically curable, but it may be managed in a way that will allow people to live with it for decades rather than months to years. Seven new chemotherapy medications have become available for treating advanced colorectal cancer in recent years. These medications can be combined with chemotherapy that is delivered directly into the liver, a place to which colon cancer commonly spreads. This combination of systemic and "localized" treatments increases the chances of longer survival and possibly a cure. Other options for treating metastatic colon cancer include radiofrequency ablation and/or surgery. Radiofrequency ablation is a procedure that allows direct heating of a tumor to kill the cancer cells. This can improve the ability of a surgeon to remove most or all of the tumor. In addition to more standard chemotherapy and radiation therapy treatments, you may benefit from new treatment options such as targeted therapies, monoclonal antibody therapy, or radiofrequency ablation. A discussion with the treating physician is strongly encouraged.

Kemeny, Nancy, et al., metastatic Colorectal Cancer: from improved survival to potential cure. Oncology. Vol. 78, No. 3-4: pp. 237-248

21. Using Oncotype Dx in Stage III Colon Cancer (Jul. 15/10)

The Oncotype DX® colon cancer test, which is currently available for treatment planning in Stage II colon cancer in the U.S., may also predict recurrence risk in Stage III colon cancer. These results were presented at the 2010 annual meeting of the American Society of Clinical Oncology. Gene expression profiling explores the patterns of genes that are active in tumor cells. Studies suggest that gene expression may provide 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 Oncotype 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 in the U.S. A similar test provides important information for patients with Stage II colon cancer. 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. The Oncotype DX test provides information about recurrence risk. To determine whether the Oncotype DX colon cancer test may also be useful for patients with Stage III colon cancer, researchers collected information from four large studies. The researchers evaluated the biological similarities and differences between Stage II and Stage III colon cancer. The results indicated that although there are some differences between Stage II and Stage III colon cancer that warrant additional evaluation, there were notable similarities for most of the 375 genes studied and for the 12-gene

Oncotype DX colon cancer Recurrence Score. In a prepared statement, the lead author of the study said, "Earlier this year physicians began incorporating Oncotype DX into clinical practice for stage II colon cancer patients. We are now conducting additional research to evaluate this test for treatment planning in stage III disease, based on the similarities observed in this study."

O'Connell MJ, et al. Comparison of molecular and pathologic features of stage II and stage III colon cancer in four large studies conducted for the development of the 12-gene colon cancer recurrence score. Presented at the 2010 annual meeting of the American Society of Clinical Oncology. June 4-8, 2010. Chicago, IL. Abstract 3503.

NUTRITION & HEALTHY LIFESTYLE

22. Exercise For Cancer Patients & Survivors is Urged (Jun. 29/10)

A panel of 13 researchers with expertise in cancer, fitness, obesity, and exercise training is spreading what they believe to be one of the most important messages for cancer patients and survivors: Avoid inactivity. The panel was convened last year by the American College of Sports Medicine (ACSM) (ACSM) to develop guidelines on exercise and physical activity in patients who are undergoing active treatment for cancer or who have completed treatment. In addition to promoting the benefits of exercise and physical activity in this group, the panel had another goal in formulating the guidelines: to promote more conversations about the need for formalized exercise programs for patients during and right after treatment—programs that will be the cancer equivalent to cardiac rehab. The benefits of exercise are well documented in a number of cancers namely in areas such as fatigue and physical functioning, both of which directly influence quality of life. While survival is the ultimate outcome measure, with an estimated 12 million cancer survivors and growing in the United States, the importance of improving quality of life has grown exponentially. According to the investigators, the evidence linking physical activity with improved quality of life in those undergoing active treatment and those who have completed it "is incredibly strong

Schmitz, Kathryn, et al., American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. Med & Science in Sports & Exercise. July 2010; Vol. 42, Issue 7: pp. 1409-1426

23. Smoking Linked to Risk of Specific Colon Cancers (Jun. 29/10)

Scientists report that smoking may boost the risk of colon cancer in older women by causing certain genetic mutations. Previous research has indicated that current and former smokers are 18% more likely to develop colorectal cancer than those who never smoked, according to a news release from the journal's publisher. It's not clear, however, how smoking and tumors are connected, especially at the molecular level. In the new study, investigators examined statistics from the Iowa Women's Health Study, focusing specifically on almost 42,000 women aged 55 to 69 who responded to a questionnaire. The researchers didn't discover much of a connection between smoking and a higher risk of colorectal cancer overall. But they did find a strong link between smoking and a specific type of colorectal cancer that's connected to genetic mutations and variations. The researchers caution that older women are especially susceptible to this subtype of colorectal cancer, so the link with smoking may not hold true for all people. Even so, the researchers wrote in the news release that new colorectal screening tests, such as those that look for genetic changes, could offer especially useful information to longtime smokers.

Boland, et al., Smoking related colorectal cancer in older women is associated with molecularly-defined DNA changes. June 29th, 2010 J of the National Cancer Institute.

24. Yoga Helps Cancer Survivors with Fatigue and Sleep (Jun. 29/10)

New research is showing a way to address both fatigue and insomnia as an aftermath in cancer patients. The study authors enrolled 410 people who had completed their treatment between 2 and 24 months before the start of the study. This group of people included very "new" cancer survivors and those who were still struggling with fatigue and insomnia up to 2 years after treatment ended. Half of the study participants were randomly selected to attend a 75 minute yoga class twice per week. The other half received regular care with no yoga. After just 4 weeks, the yoga participants gained benefit from their participation in the twice-weekly yoga sessions. Compared with the survivors who received usual care only, the yoga participants had significantly:

- Better Sleep Quality
- Less Fatigue
- Better Quality of Life

Yoga is now offered in so many places, including your local YMCA and most gyms. Free standing yoga studios are also an option. Even some cancer centers offer yoga classes for cancer survivors. If you have never practiced yoga be sure to ask your medical team if it's OK to start now. Once you get the go ahead, select the type of yoga that is right for you. Look for a class titled Hatha yoga, which is a gentle form of yoga that is ideal for beginners. Other types of yoga that can be good for beginners include

Iyengar, Kripalu,, and Anusara. No matter which type you chose, be sure to let the yoga teacher know that you are new to yoga. Also tell the teacher (instructor) that you are recovering from cancer and of any physical limitations you have. Yoga should never hurt. And you should never do any movements that don't feel good to you. Finally, keep in mind that you don't need to be a yogi master to get benefits from yoga. The participants in this study were mostly brand new to yoga. They only attended two classes per week, yet the benefits of less fatigue and better sleep became evident after just 4 weeks. If more energy sounds good to you, yoga may be what you're looking for.

<http://coloncancer.about.com/b/2010/06/28/yoga-helps-cancer-survivors-with-fatigue-and-sleep.htm>

Mustian, KM, et al., Effect of YOCAS yoga on sleep, fatigue and quality of life: A URCC CCOP randomized controlled clinical trial among 410 cancer survivors. J Clin Oncol 28: 15s, 2010. ASCO 2010: Abstract #9013

25. Higher Vitamin D Levels Offer Better Survival After Colon Cancer (Jul. 5/10)

There is a new study on vitamin D and colorectal cancer. This latest study is a little different from those that have been reported in the past. Previous studies have measured vitamin D many years prior to colon cancer diagnosis or have studied predicted (not actual) blood levels of vitamin D. This new study measured blood vitamin D levels in people newly diagnosed with colon cancer, at the time of surgery. The researchers then considered how vitamin D levels might affect survival after colon cancer. The researchers took account of other factors that can affect survival too, including age at diagnosis, gender, cancer stage, tumor location, other cancer treatments received, and whether or not the cancer had spread beyond the colon at the time of surgery. After accounting for these differences the researchers discovered three very important things about vitamin D and colon cancer survival:

1. Only 3% of the 257 people in the study had adequate levels of vitamin D. That means that 97% were deficient or insufficient in vitamin D!
2. Vitamin D levels tracked with season. Blood levels were higher in later summer and lower in spring. This makes sense, because our bodies can make vitamin D when our skin is exposed to sun of sufficient strength. This occurs mostly in the summer, when the sun is strongest and we spend more time outdoors.
3. People with blood vitamin D levels of 15 ng/ml (nanograms per milliliter) or higher had 84% better chances of surviving after colon cancer surgery compared with those who had vitamin D levels of 7 ng/ml or less.

The best way to determine if you should supplement with vitamin D is to ask your doctor to do a vitamin D test. This will tell you if your blood levels are low. If they are low, you can take a vitamin D supplement, as advised by your doctor. You can have your vitamin D levels rechecked after a few weeks to make sure they are coming up in response to the vitamin D supplements you are taking. Given that one study has shown up to 90% of people with a GI cancer are vitamin D deficient and another study found that 97% of colon cancer patients have deficient or insufficient vitamin D levels, you should talk to your doctor right away about whether you need a vitamin D supplement.

Mezawa, Hidetoshi, et al., Serum vitamin D levels and survival of patients with colorectal cancer: Post hoc analysis of a prospective cohort study. BMC Cancer 2010, 10:347.