

Does Surgery increase the risk for metastasis?

By Donald Yance

Intro and overview

The biochemical characteristics of a cancer's DNA, a mutation of our own DNA, is strongly influenced by both our internal and external environments. The environmental factors present, if favorable to the proliferation of tumor growth, can rapidly lead to the development of life-threatening cancer. "Present cancer treatment strategies are based on the assumption that a therapy may work ("response") or not work ("no-response"). However, the existing evidence suggests that current cancer treatment modalities may also have a cancer-promoting effect in part of the patients. In this paper, some relevant data are reviewed suggesting that surgery, irradiation, chemotherapy and immunotherapy can stimulate tumor growth / metastatic spread and decrease survival of patients in certain subgroups. Thus, results of cancer treatment may be improved by detection and use of biomarkers that correlate with positive or negative therapeutic effects." Moreover, ignoring biomarkers that correlate with positive or negative therapeutic effect may not be compatible anymore with the ethical principle "First Do No Harm".

Dainius Characiejus & Jasmina Hodzic & John J. L. Jacobs, "First do no harm" and the importance of prediction in oncology, EPMA Journal (2010) 1:369–375

There is evidence that supports that removal of a primary tumor may not extend life or increase quality of life. It is actually possible that removal of a cancerous tumor can indeed spread cancer. Removing a tumor does not change the internal terrain of the body, thereby making it less favorable for a cancer to proliferate, in fact in some cases, removing a primary tumor can affect changes in the internal environment that cause further tumor growth and metastases. I am not stating surgery isn't very important and part of the toolbox for cancer treatment but I am saying we need to plan carefully when surgery should happen and prep and person by both strengthening them with anabolic-immune-enhancing botanicals and immunonutrients, as well as, target the cancer systemically for an appropriate period of time before, as well as, after the surgery.

What Eli Jones said about surgery and cancer more than one hundred years ago

The great cancer physician, Eli G. Jones, wrote a book in 1894, on cancer, called "Cancer – Its causes, symptoms, and treatments". "A surgeon can only cut out what is seen and felt under the knife, while millions of cancer cells grow and multiply in the blood, the nuclei of future cancer. Another fact that the surgeon forgets is that every operation is a shock to the nervous system, it lowers the nerve power, weakens the power of resistance to disease and thus encourages the invasion of cancer."

Here is an entire section taken from Chapter 2, entitled, "Surgery not a Cure for Cancer."

There are about 50,000 people who die of cancer in the United States annually. From my own experience in the treatment of cancer in all its forms, for forty years, I feel confident that ninety-five per cent of these cases could have been saved without an operation. Over the tombstones of most of them might be written, "BUTCHERED IN THE NAME OF SCIENCE." For the past 200 years the great mass of the medical profession have considered cancer as a local disease, and they have made it their practice to cut out everything that looks like a cancer.

Dr. Walsh, in his able work on cancers, says: "The knife can neither be regarded as a means of curing cancer or of prolonging the existence of the person afflicted with the disease." Dr. Thomas W. Cooke, surgeon of the Cancer Hospital, London, England, says: "From 1851 to 1863 there were 413 cases of cancer operated on at the Cancer Hospital, London, England. The average time before the cancer returned was only 6 1/2 months." Dr. Monroe, of Scotland, operated on "sixty cases of cancer; at the end of two years only four out of the sixty operations were successful". In 1896 I kept a record of fifty cases of cancer of the tongue that had been operated upon, and not a single cure was affected. Dr. James Wood of the Royal College, London, said: "Gentlemen, I have operated on some thousand cases of cancer and they all returned but six, and they were not cancer." Sir Benjamin Brodie (one of the fathers in surgery) said, after he had removed 500 cancers of the breast, that "he would not remove another without telling the patient that the operation would not prolong her life."

Sir James Paget, one of England's greatest physicians, says in speaking of cancer, "the number of cases in which cancer does not return is not more than one in Five Hundred." In my own practice about four out of five cases of cancer that come to me have had a surgical operation, and the cancer had returned worse than it was before.

About one hundred years ago the early fathers of the Botanic School of Medicine considered cancer as a blood or constitutional disease and treated it as such and cured it. No form of purely local treatment will ever cure this malady, because it is in the blood and must be reached through the blood. In 1869 I treated my first case of cancer. I called it a blood disease. I treated it with our simple botanic remedies and cured it.

If I ever had any faith in a surgical operation as a cure for cancer it has been rudely shaken by my daily contact with victims of cancer that have been operated upon with the result that the cancer has returned in a worse state than at first. I have been forced to the conclusion that an operation never cures the disease, but actually hastens the death of the victim. In this State, I saw a case of cancer of the breast that had been operated on three times; the last time the surgeon made a thorough examination with the microscope, after the operation, and told the lady that he would "guarantee that the cancer would never return." In six months the cancer was doing business at the old stand.

I saw a case of cancer of the breast from New York State that had been cut out eight times and the disease had returned worse than ever. Another lady had a cancer of the breast operated upon twelve times and the cancer finally caused her death. In another case I saw a young man, who had a swelling come in his groin. The doctors cut it out; it returned and then another operation, and so on until he had been operated upon four times. At the time I saw the case the leg above the knee was one mass of sarcoma. He was past cure. I met with a lady in this State who had a cancer near the eye. It had been cut out four times and given up as past cure, but I cured it and that was seven years ago. I met with a case of cancer where the breast had been removed; it returned and another operation removed the arm of the affected side. Then death closed the scene.

Time and again I have seen cases where all the breast had been removed and all the glands under the arm of the affected side, and still the cancer returned. I recall cases of cancer of the uterus that had been operated on from one to three times and finally caused the death of the patient. I have had to listen to many a tale of woe from patients, who have told me with tears running down their cheeks that their physicians had told them. if they "would have their cancer cut out that it would never return". Any doctor who makes such a statement as that must be either a knave or a fool; let us be charitable and think that it must be the latter. For no doctor who has had any experience with cancer would ever make a promise of that kind. It has been the hardest work of my life to make some doctors realize that the growth they see is only the effect, and that back of that lies the cause; and the cause must be removed before we can cure the cancer.

May God hasten the day when it will be considered a crime to cut out a cancer. After forty-three years' experience with cancer I can honestly say that I have never seen a genuine case of cancer permanently cured by a surgical operation. To cut out a cancer is the worst form of malpractice, for it is only trying to remove the effect without touching the cause. From an extensive correspondence with physicians from every State in the Union I find that the rank and file of the profession are tired and disgusted with operations for cancer, for they have seen them return time and time again. They are more than anxious to find a better and saner method of treatment for cancer that offers at least some hope of a cure.

IS THE CURRENT TREATMENT OF CANCER SELF-LIMITING IN THE EXTENT OF ITS SUCCESS?

J Int Acad Preventive Medicine, 6 (1) 23 – 39, 1979).

Ernst H. Krokowski, MD, PhD. (1926 - 1985), Professor of Medicine (Radiology) and Chief of the Central Inst. of Radiology of Kassel Hospital in Germany.

“Gregl found in his extensive studies of patients with mammary carcinoma that elderly women with an untreated mammary carcinoma live longer than women of the same age after palliative or radical therapy. His co-worker, Mueller, concludes from these studies that elderly women with mammary carcinoma should not be treated at all.”

“In very many patients whose tumor had been removed by surgery and radiation and who are, therefore, believed to be free of cancer, metastases occur frequently at a certain time after the operation.”

Bashford E, Murray JA, Cramer W. The natural and induced resistance of mice to the growth of cancer. *Proc R Soc Lond* 1907; 79: 164–187.

Marie P, Clunet J. Fréquences des métastases viscérales chez les souris cancéreuses après ablation chirurgicale de leur tumeur. *Bull Assoc Franç pour l'étude du cancer* 1910; 3: 19–23

Animal research dating back as far as 100 years demonstrated that implanted tumors, which if allowed to develop naturally rarely resulted in spontaneous metastases, frequently produced metastases if the primary implant was incompletely excised.

“This pessimistic attitude remained quite widely accepted until the middle of 19th century, when, on the basis of the arguments suggested by Virchow, the Halsted operation was adopted as default therapy worldwide. Twentieth-century progress in antisepsis, anesthesia and surgery fueled aggressive surgical treatments and operations even more extensive than the radical mastectomy were explored. In spite of all these surgical efforts and patient suffering, however, 30% of resected node-negative and 75% of node-positive patients still developed distant metastases and succumbed.”

Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The effects of surgery on tumor growth: a century of investigations. *Ann Oncol*. 2008 Jun 10

Parallels between wound healing and cancer

“Inflammation is a crucial function of the innate immune system that protects host tissues against dangerous insults that are detrimental to tissue homeostasis, including wound damage and pathogen invasion. Acute inflammation, as triggered by wounding, is a rapid and self-limiting process: chemical mediators are induced in a tightly regulated sequence, and innate immune cells move in and out of the affected area, destroying infectious agents, and delivering growth factors and other signals that aid in repairing the damaged tissue.

Medzhitov R (2008) Origin and physiological roles of inflammation. *Nature* 454: 428–435.

Martin P, Leibovich S. J (2005) Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol* 15: 599–607.

However, when innate immunity goes awry, inflammation does not always resolve, and it is believed that chronic, “smouldering,” and often subclinical inflammation can be the root cause of many human pathologies, including cancer. Because of difficulties in predicting when and where transformed cells may arise in an organism, very little is currently known about the earliest events whereby host tissues respond to somatic cell transformation prior to the emergence of any sign of malignant progression. When does the host first recognize transformed cells, and how do they interact? Answering this question begs a model that allows easy live, in vivo observation of these events.

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? *Lancet* 357: 539–545.

Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. *Nature* 454: 436–444.

Coussens L. M, Werb Z (2002) Inflammation and cancer. *Nature* 420: 860–867.

Karin M, Lawrence T, Nizet V (2006) Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 124: 823–835.

Activation of leukocytes at very early stages in larvae carrying a transformed cell burden. Locally, we see recruitment of neutrophils and macrophages by 48 h post-fertilization, when transformed cells are still only singletons or doublets, and soon after this we see intimate associations between immune and transformed cells and frequent examples of cytoplasmic tethers linking the two cell types, as well as engulfment of transformed cells by both neutrophils and macrophages. We show that a major component of the signal drawing inflammatory cells to oncogenic HRASG12V-transformed cells is H₂O₂, which is also a key damage cue responsible for recruiting neutrophils to a wound. Our short-term blocking experiments show that preventing recruitment of immune cells at these early stages results in reduced growth of transformed cell clones and suggests that immune cells may provide a source of trophic support to the transformed cells just as they do at a site of tissue repair. These parallels between the inflammatory responses to transformed cells and to wounds reinforce the suggestion by others that cancers resemble non-healing wounds.

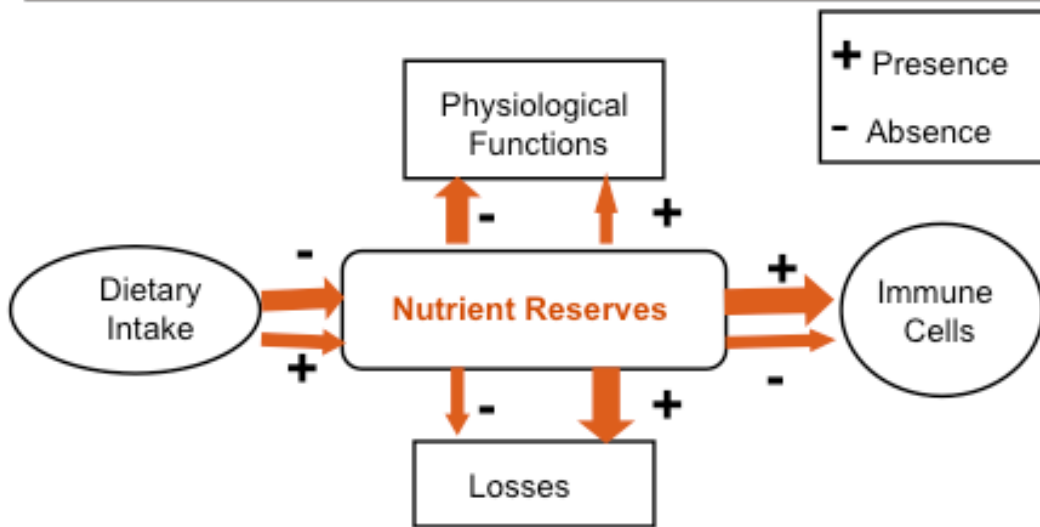
Yi Feng, Cristina Santoriello, Marina Mione, Adam Hurlstone, Paul Martin, *PLoS Biology*: Live Imaging of Innate Immune Cell Sensing of Transform...sh Larvae: Parallels between Tumor Initiation and Wound Inflammation

Activities of the major players in wound healing

Cell type	Source	Timing and behavior
Keratinocytes	Epidermal wound edges and cut appendage stumps	Migration commences after a brief lag phase
Fibroblasts/myofibr oblasts	Connective tissue wound edges and fibrocytes from circulation	Invasion to form wound granulation tissue commences early, but transformation into myofibroblasts is later
Endothelial cells	Nearby blood vessels	Vasculature near to wound site becomes activated rapidly to allow diapedesis, but sprouting is later
Platelets	Spill from damaged blood vessels	Immediately at the site of tissue damage
Mast cells	Small numbers resident in tissue; others by diapedesis from adjacent vessels	Appear to have an early role in regulating the later inflammatory response by neutrophils
Neutrophils	Diapedesis from adjacent vessels	Earliest of the leukocytes to derive from the blood
Macrophages	Some tissue-resident cells but majority derive from blood-borne monocytes	Secondary influx from the blood after neutrophils have killed the immediate foreign-organism invaders

Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol.* 2005 Nov;15(11):599-607. Epub 2005 Oct 3.

Immune Challenge from Surgery on Nutrient Reserves

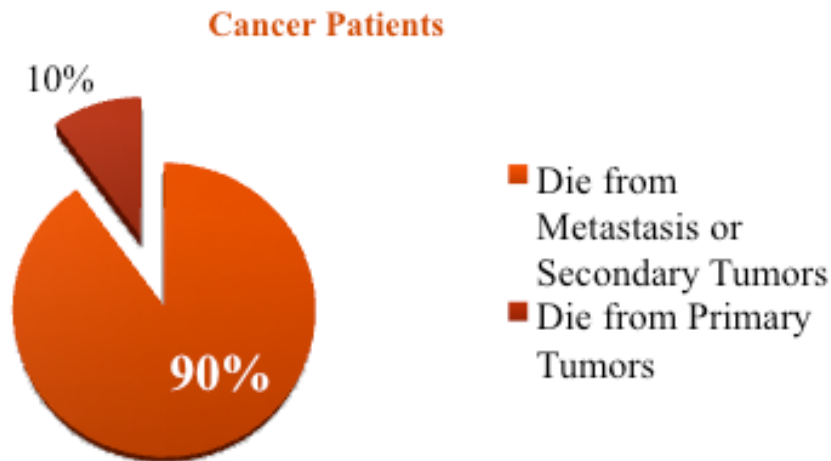


Tumor dormancy and surgery-driven interruption of dormancy in breast cancer

A recent review paper on breast cancer and surgery summarized that “Primary tumor removal, usually considered intrinsically beneficial, can perturb metastatic homeostasis, and for some patients results in the acceleration of metastatic cancer. The continuous-growth model is required to yield to an interrupted-growth model, the implications of which are episodes of tumor dormancy. This Review analyzes the recent evolution of two paradigms related to the development of breast cancer metastases. The evolution of the paradigms described herein is supported by a growing body of findings from experimental models, and is required to explain breast cancer recurrence dynamics for patients undergoing surgery with or without adjuvant chemotherapy.”

Demicheli R, Retsky MW, Hrushesky WJ, Baum M. Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures. *Nat Clin Pract Oncol.* 2007 Dec;4(12):699-710. Review.

90% of Cancer Patients Die from Metastasis or Secondary Tumors



The ETMS Approach

My twenty years plus experience with cancer has also brought me to the same belief that after surgery, other than in cancers of a more benign-like behavior, such as a slow-growing basal cell cancer on the skin, or a breast tumor with a full pathology of nothing but favorable markers, cancer will not only return, but spread, and become more aggressive. This is especially true in the more aggressive cancers, such as renal cell (Kidney), and pancreatic. If one is going to have surgery, and must, they should begin with the formulation of a thorough plan. This consists of an aggressive systemic protocol that targets the health of the person, the specific nature of the cancer, and is based upon natural compounds that suppress angiogenesis while simultaneously promoting healing. There is a place for surgery in cancer treatments but in today's medical oncology practice it is not reserved for the few cases in which it is the most favorable option. If one has been successful with employment of a balanced aggressive systemic treatment plan, i.e. shrinking the tumor and building up the healing energy, then surgery can successfully be employed without generating a more metastatic environment.

Three reasons for implementing a systemic program first and letting it take hold are:

- 1) If you have been successful at shrinking the tumor, or removing it entirely, your long-term prognosis is good; but if you remove the tumor, then start a systemic program, you have no way of knowing how you are affecting the cancer.

- 2) If you have shrunk the tumor, surgery becomes easier, less invasive, and often spares the need for reconstruction; the smaller the tumor the less aggressive the surgery often needs to be.
- 3) Because cancer is a systemic disease, treating upfront systemically reduces the risk of metastasis.

Surgery up-regulates several growth factors necessary for angiogenesis, as well as inflammatory pathways, such as COX-2 and LOX-5. These compounds are up-regulated post-surgery for the purpose of angiogenesis, an integral part of the body's innate healing process. With the discovery of the role COX-2 plays in angiogenesis, modern medicine is just beginning to perhaps recognize this. In addition, surgery causes mutations of important, cancer-suppressor genes, most notably the nm23 gene. The primary tumor has been shown to suppress angiogenesis in its distant metastasis. Surgery also weakens the vitality of the patient. The energy that is needed to heal from surgery is the same energy that is needed to control/suppress cancer. Often the body has to make compromises with regard to direction of energy. This leads to a weakened state of the cancer patient following surgery, which in turn leaves them more vulnerable to the spread of cancer.

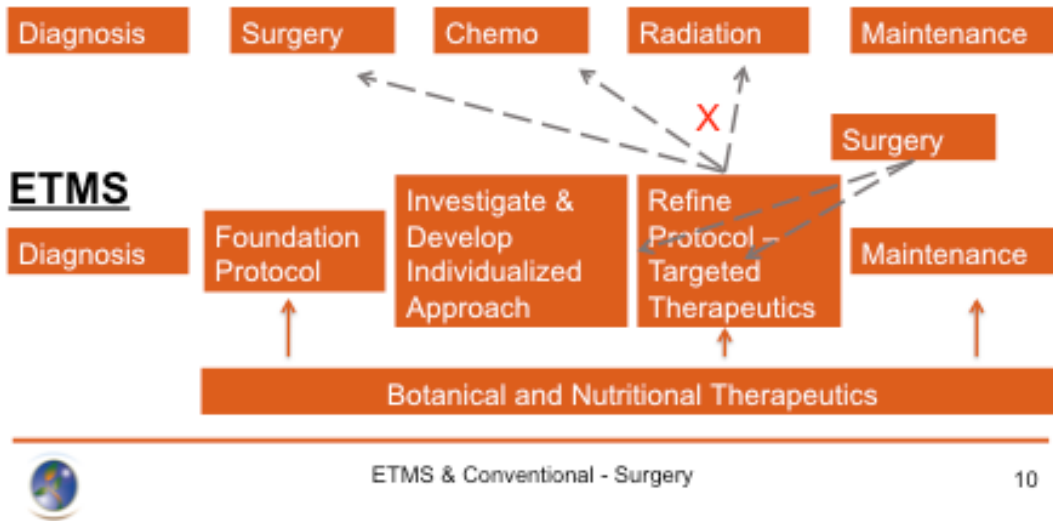
Always do a pre and post surgery protocol using adaptogens, anabolic nutrients and nutrients that promote healing and inhibit infection. These include companion adaptogens, immune-modulators, enzymes, etc.

Adaptogens, such as Panax ginseng, have an ability to promote healing, build vitality, inhibit cancer growth and suppress angiogenesis simultaneously. Panax ginseng has recently been shown to promote angiogenesis for healing, while at the same time suppressing cancer-related angiogenesis.

Sengupta, PhD; Sue-Anne Toh, MBChB; Lynda A. Sellers, PhD; Jeremy N. Skepper, PhD; Pieter Koolwijk, PhD; Hi Wun Leung, PhD; Hin-Wing Yeung, PhD; Ricky N.S. Wong, PhD; Ram Sasisekharan, PhD; Tai-Ping D. Fan, PhD, Modulating Angiogenesis The Yin and the Yang in Ginseng Shiladitya, Circulation. 2004;110:1219-1225.

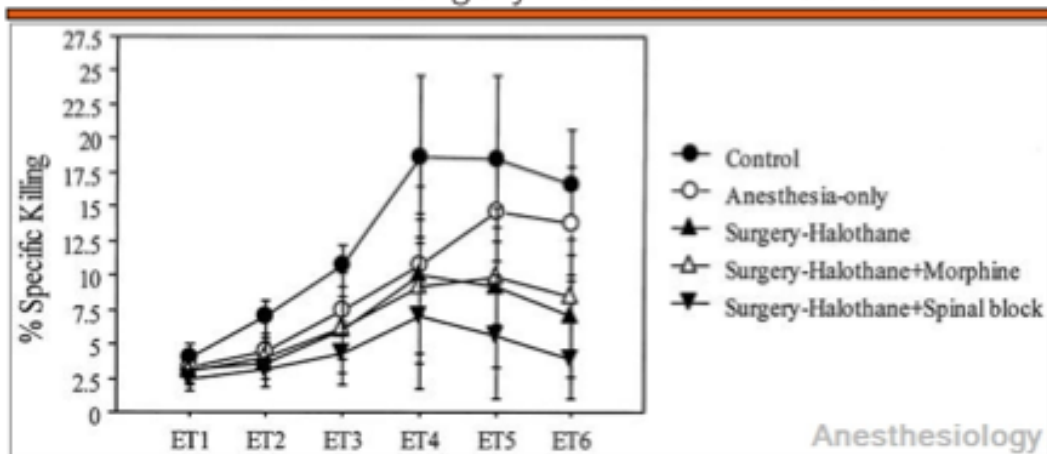
Standard vs. ETMS Approach

Standard Medical Approach



“Food for thought” - Some recent research studies confirming the detrimental effects of surgery in cancer include an overall systemic lowering on Natural Killer cells, the most important cells for fighting cancer.

The Tumor-promoting Effect of Surgery by Spinal Blockade – Surgery Reduces NK Cells



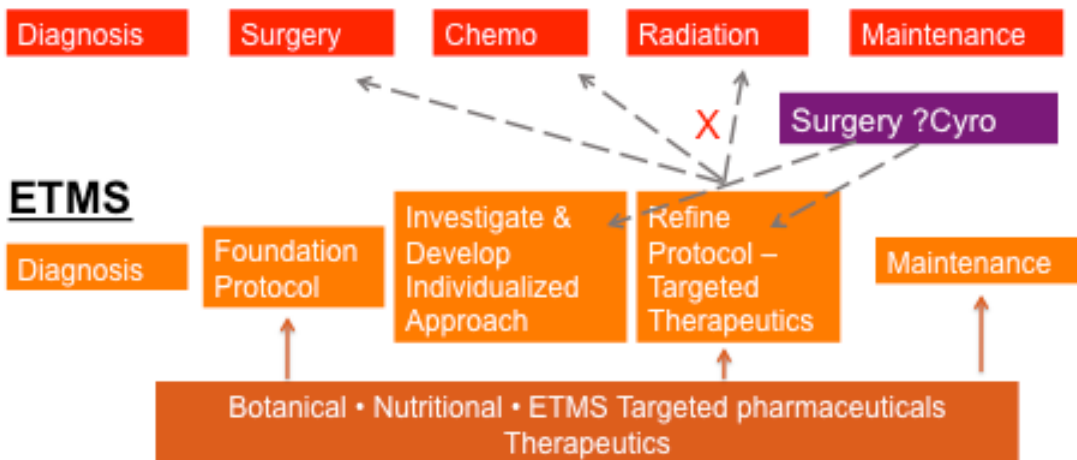
Effects of anesthesia and surgery on natural killer (NK) cytotoxic activity (expressed as percent specific killing at six effector-to-target [ET] ratios), assessed 5 h after the beginning of surgery. Surgery suppressed NK activity compared with the control group, with no significant difference between the various anesthetic regimens.

Anesthesiology. 94(6):1066-1073, June 2001.

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Standard vs. ETMS Approach

Standard Medical Approach



ETMS & Conventional - Surgery

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Evidence that stress and surgical interventions promote tumor development by suppressing natural

Stress and surgery have been suggested to compromise host resistance to infectious and malignant diseases in experimental and clinical settings. Because stress affects numerous physiological systems, the role of the immune system in mediating such effects is unclear. In the current study, we assessed the degree to which stress-induced alterations in natural killer (NK) cell activity underlie increased susceptibility to tumor development in F344 rats. Two stress paradigms were used: forced swim and abdominal surgery. Host resistance to tumor development was studied using 3 tumor models syngeneic to inbred F344 rats: CRNK-16 leukemia and the MADB106 mammary adenocarcinoma, both sensitive to NK activity, and the NK-insensitive C4047 colon cancer. Swim stress increased CRNK-16-associated mortality and metastatic development of MADB106 but not metastasis of C4047 cells. In both stress paradigms, stress suppressed NK activity (NKA) for a duration that paralleled its metastasis-enhancing effects on the MADB106 tumor. In vivo depletion of large granular lymphocyte/NK cells abolished the metastasis-enhancing effects of swim stress but not of surgical stress. Our findings indicate that stress-induced suppression of NKA is sufficient to cause enhanced tumor development. Under certain stressful conditions, suppression of NKA is the primary mediator of the tumor-enhancing effects of stress, while under other conditions, additional factors play a significant role. Clinical circumstances in which surgical stress may induce enhanced metastatic growth are discussed.

Ben-Eliyahu S, Page GG, Yirmiya R, Shakh G. Evidence that stress and surgical interventions promote tumor development by suppressing natural, *Int J Cancer*. 1999 Mar 15;80(6):880-8.

Example: Surgery and Cancer

PROS

- Remove/reduce tumor burden/immunological strain
- Ability to do molecular profiling (only need biopsy)
 - For targeted therapy
 - For formulating an effective individualized systemic protocol
- Ability to do tumor sensitivity and resistance testing

CONS

- Systemic stress - impact of Life-Force burden on recovery.
- Reduction in NK cells/lost nm 23 gene (anti-metastatic)
- ↑ Inflammatory - tumor-promoting Cytokines
- ↑ Angiogenic - growth factors
- ↑ Nutrient demands - Zinc, ARG, Glutamine, Vitamin C, E etc.



Ref. DY Surgery in Cancer 01-2012

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Immunonutrition: A Foundational Piece of the ETMS

- The potential to modulate immune system activity by interventions with specific nutrients is called immunonutrition.
 - Applied when an altered supply of nutrients is used to modify inflammatory/immune responses.
 - Major surgery, radiation therapy, and/or chemotherapy is followed by a period of immunosuppression that increases the risk of morbidity and mortality due to allostatic overload, which can lead to infection.
 - Improving immune function during this period will improve a person's ability to inhibit infection, recover quickly and fully, and reduce the risk of reoccurrence.
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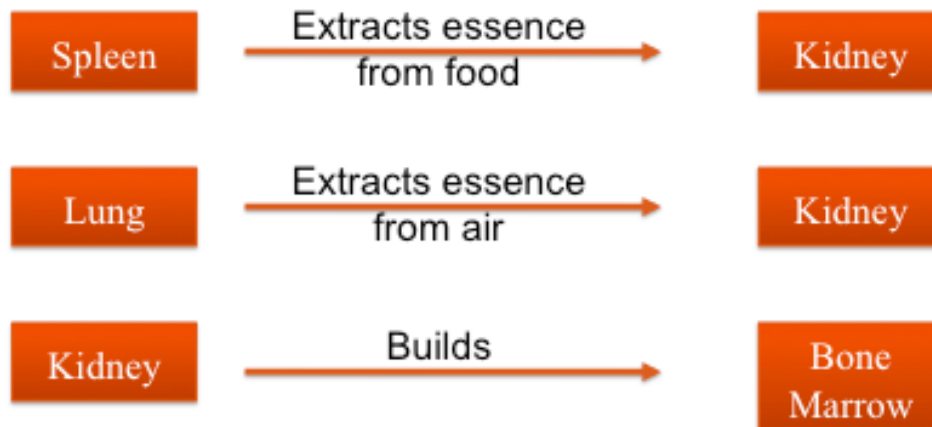


Immunonutrition: A Foundational Piece of the ETMS (continued)

- Anabolic and adaptogenic plant-based remedies together with immunonutrition are foundational for building the “Internal Energy Force.”
- The herbs without the nutrients or the nutrients without the herbs will often be far less effective than the two approaches working together.



Bone Marrow Enhancement Boost the Kidney & Spleen Systems



Research studies

Colon cancer

Removal of a primary colorectal tumor resulted in an increase in metabolic activity and liver metastasis. Concomitantly, levels of angiostatin and endostatin in urine and plasma, respectively, dropped. This finding indicates that the primary tumor suppressed angiogenesis in its distant metastasis, and that removal of the primary lesion caused a flare-up in vessel neoformation and, thus, enhanced metabolic activity in its liver metastasis.

Peeters CF, de Geus LF, Westphal JR, de Waal RM, Ruiter DJ, Wobbes T, Oyen WJ, Ruers TJ. Decrease in circulating anti-angiogenic factors (angiostatin and endostatin) after surgical removal of primary colorectal carcinoma coincides with increased metabolic activity of liver metastases. *Surgery*. 2005 Feb;137(2):246-9.

Colon cancer

In animal models, explosive growth of metastases after removal of the primary tumor has been attributed to abolishment of angiogenesis inhibition. We investigated the influence of (removal of) the primary tumor on vascularization of liver metastases in human colorectal cancer patients. We analyzed vascular density in synchronous liver metastases from patients with the primary tumor *in situ*, in synchronous metastases from patients

with the primary tumor resected and in metachronous metastases. In a limited number of cases, biopsies from metastases from the same patient before and within 3 months after resection were analyzed. In addition, vascular density in metastases was compared to the vascular density in the corresponding primary tumor. Peritumoral and intratumoral vascular density were determined by staining for endothelial antigens CD31 and CD34, respectively. Both peritumoral and intratumoral vascular density were elevated in synchronous metastases from patients with the primary tumor removed compared to synchronous metastases from patients with the primary tumor *in situ*. Comparable results were observed in patients with metachronous metastases. An increase in vascular density after resection of the colorectal malignancy was also observed in biopsies taken from the same patient before and after tumor resection. Remarkably, vascular density in the liver metastases was always lower than that in the corresponding primary tumor. Our data show for the first time in humans that the presence of a primary tumor is correlated with decreased vascularization of its distant metastases. Resection of the primary tumor results in an increased vascularization of metastatic lesions.

Charlotte F.J.M. Peeters, Johan R. Westphal, Robert M.W. de Waal, Dirk J. Ruiter, Theo Wobbes, Theo J.M. Ruers, **Vascular density in colorectal liver metastases increases after removal of the primary tumor in human cancer patients**, *Int J Cancer*. 2004 Nov 20;112(4):554-9. Department of Pathology, University Medical Centre Nijmegen, Nijmegen, The Netherlands, Department of Surgical Oncology, University Medical Centre Nijmegen, Nijmegen, The Netherlands, Charlotte F.J.M. Peeters (c.peeters@pathol.umcn.nl)

Colon cancer

To study the factors of colorectal cancer (CRC) after radical resection to provide data predicting the prognosis of the patients. **METHODS:** 120 cases of CRC were collected in this study. Medical clinical records and 5-year follow-up data were reviewed. Streptavidin-peroxidase immunohistochemical technique was used to detect the expression of p53, C-erbB-2, nm23-H(1) and Ras on formalin-fixed, paraffin embedded sections of CRC from the 120 patients. **RESULTS:** Results showed that the rates of positive expression of p53, C-erbB-2, Ras and nm23-H(1) were 62.5% (75/120), 25.8% (31/120), 80.0% (96/120) and 60.8% (73/120) respectively in the CRC tissue. All pathological variables and biological markers were analyzed with Cox regression model ($\alpha = 0.05$). Eight distinguished prognostic factors were identified in the univariate analysis as: macroscopic configuration, histology grade, depth of invasion of intestinal, lymph nodes metastasis, Dukes' classification, p53, Ras and nm23-H(1). The results of multivariate analysis ($\alpha = 0.05$) indicated that the independent prognostic factors were Dukes' classification, p53 and nm23-H(1) ($P = 0.000$), with relative risk of 3.06, 6.02 and 0.40, respectively. A prognostic model: $h(t, x) = h(0)(t)\exp(-0.9269X(14) + 1.1197X(10) + 1.7948X(11))$ was established. Sensitivity, specificity agreement and reliability of the model and Kappa were 79.1%, 83.0%, 80.8% and 0.62, respectively. **CONCLUSION:** Dukes' classification, p53 and nm23-H(1) seemed to be independent and important prognostic factors. This prognostic model could be used to evaluate the prognosis of patients with CRC by clinicians.

Yang YF, Li PZ, Liang XB, Han XL, Li YP, Cong J., factors of colorectal cancer (CRC) after radical resection to provide data predicting the prognosis of the patients., [Article in Chinese], *Zhonghua Liu Xing Bing Xue Za Zhi*. 2005 Mar;26(3):214-7. Department of Epidemiology, Shanxi Medical University, Taiyuan 030001, China.

Rapid outgrowth of metastases after removal of the primary tumor has been described in several mouse models. Loss of primary tumor-induced inhibition of angiogenesis in the metastases has been suggested as the underlying cause. Accordingly, we recently demonstrated that vascular density in human colorectal liver metastases increases after primary tumor resection. Here, we investigate whether this increase in vascular density has, in its turn, effects on the tumor growth of the liver metastases. We analyzed tumor growth in synchronous liver metastases from patients with the primary tumor in place, in synchronous metastases from patients with the primary tumor resected and in metachronous metastases. Tumor growth was studied by assessing the percentage of cells undergoing apoptosis by activated caspase-3 staining, and the percentage of proliferating cells by Ki-67 staining. While the percentage of proliferating cells within the metastases showed a modest increase after primary tumor resection, a significant decrease in the percentage of apoptotic cells was observed. Taken together, an increased net tumor growth of the metastases occurred after primary tumor resection. This acceleration of tumor growth could be confirmed by studying biopsies taken from the same patient before and after tumor resection. Our data show that in human cancer patients, a primary tumor may inhibit the growth of its liver metastases.

Peeters CF, de Waal RM, Wobbles T, Westphal JR, Ruers TJ. Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. *Int J Cancer*. 2006 Sep 15;119(6):1249-53.

Colorectal cancer: Recurrence after successful surgery

To explore the risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. **METHODS:** Specimens of middle and lower rectal carcinoma from 56 patients who received curative resection at the Department of General Surgery of Guangdong Provincial People's Hospital were studied. A large slice technique was used to detect mesorectal metastasis and evaluate circumferential resection margin status. The relations between clinicopathologic characteristics, mesorectal metastasis and circumferential resection margin status were identified in patients with local recurrence of middle and lower rectal carcinoma. **RESULTS:** Local recurrence of middle and lower rectal carcinoma after curative resection occurred in 7 of the 56 patients (12.5%), and was significantly associated with family history ($c2 = 3.929$, $P = 0.047$), high CEA level ($c2 = 4.964$, $P = 0.026$), cancerous perforation ($c2 = 8.503$, $P = 0.004$), tumor differentiation ($c2 = 9.315$, $P = 0.009$) and vessel cancerous emboli ($c2 = 11.879$, $P = 0.001$). In contrast, no significant correlation was found between local recurrence of rectal carcinoma and other variables such as age ($c2 = 0.506$, $P = 0.477$), gender ($c2 = 0.102$, $c2 = 0.749$), tumor diameter ($c2 = 0.421$, $P = 0.516$), tumor infiltration ($c2 = 5.052$, $P = 0.168$), depth

of tumor invasion ($c2 = 4.588$, $P = 0.101$), lymph node metastases ($c2 = 3.688$, $P = 0.055$) and TNM staging system ($c2 = 3.765$, $P = 0.152$). The local recurrence rate of middle and lower rectal carcinoma was 33.3% (4/12) in patients with positive circumferential resection margin and 6.8% (3/44) in those with negative circumferential resection margin. There was a significant difference between the two groups ($c2 = 6.061$, $P = 0.014$). Local recurrence of rectal carcinoma occurred in 6 of 36 patients (16.7%) with mesorectal metastasis, and in 1 of 20 patients (5.0%) without mesorectal metastasis. However, there was no significant difference between the two groups ($c2 = 1.600$, $P = 0.206$). **CONCLUSION:** Family history, high CEA level, cancerous perforation, tumor differentiation, vessel cancerous emboli and circumferential resection margin status are the significant risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. Local recurrence may be more frequent in patients with mesorectal metastasis than in patients without mesorectal metastasis.

Wu ZY, Wan J, Zhao G, Peng L, Du JL, Yao Y, Liu QF, Lin HH. Risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. *World J Gastroenterol.* 2008 Aug 14;14(30):4805-9.

Risk factors for local recurrence of middle and lower rectal carcinoma after curative resection

To explore the risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. **METHODS:** Specimens of middle and lower rectal carcinoma from 56 patients who received curative resection at the Department of General Surgery of Guangdong Provincial People's Hospital were studied. A large slice technique was used to detect mesorectal metastasis and evaluate circumferential resection margin status. The relations between clinicopathologic characteristics, mesorectal metastasis and circumferential resection margin status were identified in patients with local recurrence of middle and lower rectal carcinoma. **RESULTS:** Local recurrence of middle and lower rectal carcinoma after curative resection occurred in 7 of the 56 patients (12.5%), and was significantly associated with family history ($c2 = 3.929$, $P = 0.047$), high CEA level ($c2 = 4.964$, $P = 0.026$), cancerous perforation ($c2 = 8.503$, $P = 0.004$), tumor differentiation ($c2 = 9.315$, $P = 0.009$) and vessel cancerous emboli ($c2 = 11.879$, $P = 0.001$). In contrast, no significant correlation was found between local recurrence of rectal carcinoma and other variables such as age ($c2 = 0.506$, $P = 0.477$), gender ($c2 = 0.102$, $c2 = 0.749$), tumor diameter ($c2 = 0.421$, $P = 0.516$), tumor infiltration ($c2 = 5.052$, $P = 0.168$), depth of tumor invasion ($c2 = 4.588$, $P = 0.101$), lymph node metastases ($c2 = 3.688$, $P = 0.055$) and TNM staging system ($c2 = 3.765$, $P = 0.152$). The local recurrence rate of middle and lower rectal carcinoma was 33.3% (4/12) in patients with positive circumferential resection margin and 6.8% (3/44) in those with negative circumferential resection margin. There was a significant difference between the two groups ($c2 = 6.061$, $P = 0.014$). Local recurrence of rectal carcinoma occurred in 6 of 36 patients (16.7%) with mesorectal metastasis, and in 1 of 20 patients (5.0%) without mesorectal metastasis. However, there was no significant difference between the two groups ($c2 = 1.600$, $P = 0.206$). **CONCLUSION:** Family history, high CEA level, cancerous perforation, tumor differentiation, vessel cancerous emboli and circumferential resection margin status are

the significant risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. Local recurrence may be more frequent in patients with mesorectal metastasis than in patients without mesorectal metastasis.

Wu ZY, Wan J, Zhao G, Peng L, Du JL, Yao Y, Liu QF, Lin HH. Risk factors for local recurrence of middle and lower rectal carcinoma after curative resection. *World J Gastroenterol.* 2008 Aug 14;14(30):4805-9.

Overexpression of Tyrosine Kinase B Protein as a Predictor for Distant Metastases and Prognosis in Gastric Carcinoma.

Tyrosine kinase B (TrkB) is associated with aggressive behavior and poor prognosis in various cancers. Here we examined the association between TrkB expression and distant metastases/prognosis in gastric carcinoma (GC). **Patients and Methods:** We analyzed TrkB expression in 161 GC patients by immunohistochemistry and Western blot analysis. The correlation of TrkB mRNA and protein expression levels was examined in 10 patients by RT-PCR assay. **Results:** TrkB expression was of level 1 in 97 (60.2%) and level 2 in 64 (39.8%) patients. Patients with level 2 expression had a significantly higher incidence of distant metastases ($p < 0.0001$), well-differentiated tumors ($p < 0.005$), deeper depth of invasion ($p < 0.005$) and poorer disease-free and overall survival ($p < 0.0001$ each) compared to patients with level 1. Multivariate analysis identified the level of TrkB expression as an independent prognostic factor for both disease-free and overall survival ($p < 0.01$ and $p < 0.0001$, respectively). Both lymph node metastasis (odds ratio = 10.7) and TrkB expression (odds ratio = 9.3) were independent predictors of distant metastases. **Conclusion:** A high level of TrkB expression was observed in well-differentiated GC subtypes and is a predictor for distant metastases and prognosis in GC.

Zhang Y, Fujiwara Y, Doki Y, Takiguchi S, Yasuda T, Miyata H, Yamazaki M, Ngan CY, Yamamoto H, Ma Q, Monden M. Overexpression of Tyrosine Kinase B Protein as a Predictor for Distant Metastases and Prognosis in Gastric Carcinoma. *Oncology.* 2008 Aug 22;75(1-2):17-26.

Breast Cancer: Operation May Trigger Growth Of Other Tumors

Could surgery to remove breast cancer tumors actually increase the risk of a relapse? A small group of respected researchers suspects that in a significant number of women, surgery itself may trigger the rapid growth of smaller tumors elsewhere in the body. "With (surgical) intervention, we may in some cases make things worse," says Michael Retsky, a researcher at Harvard Medical School and Children's Hospital in Boston. Retsky argues that more than half of breast cancer relapses may be accelerated by surgery and says the phenomenon may apply to surgery for other types of cancer. The director of breast cancer research and treatment at Memorial Sloan-Kettering Cancer Center in New York, Norton is planning lab studies to examine the effects of surgery on secondary, unremoved tumors. If breast cancer operations do turn out to stimulate tumors, researchers will have to develop techniques to counteract the effect.

Demicheli R, Bonadonna G, Greco M, Hrushesky WJ, Moliterni A, Retsky MW, Valagussa P, Zambetti M., Comment to Anderson WF, Jatoi I, Devesa SS: Distinct Breast Cancer Incidence and Prognostic Patterns in the NCI's SEER Program: Suggesting a Possible Link Between Etiology and Outcome. *Breast Cancer Res Treat* 90:127-137, 2005. *Breast Cancer Res Treat*. 2006 May 10

Breast cancer

This historical perspective on breast cancer tells us how and why certain therapeutic eras have reached ascendancy and then declined. Therapeutic revolutions occur after a crisis develops when there is a general recognition that clinical interventions are not producing positive results predicted by the prevailing paradigm. The attitude of pre-modern surgeons was influenced by the very real possibility of doing more harm than good by operating upon women with breast cancer. Up until Halsted, the general consensus was clearly that, unless forced by the circumstances, surgical resection should be avoided for disease much more advanced than very early stage tumours (the cacoethesis of Celsus). Twentieth century progress in antisepsis, anaesthesia, and surgery changed this point of view. The first three quarters of that century saw more and more aggressive operations performed while the last quarter century reversed this trend, with reduction of the size of breast cancer operations based largely on the teachings of Fisher. A new crisis is upon us now in that trials of early detection have resulted in unexpected disadvantages to certain subgroups and there is previously unreported structure in early hazard of relapse, clinical data that suggests the act of surgery might accelerate the appearance of distant metastases. The explanation we propose that agrees with these results, as well as physicians of antiquity, is that surgery can induce angiogenesis and proliferation of distant dormant micrometastases, especially in young patients with positive nodes.

Baum M, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? *Eur J Cancer*. 2005 Mar;41(4):508-15. Epub 2005 Jan 18.

Breast cancer

Retsky MW, Demicheli R, Hrushesky WJ. Screening and breast cancer. *N Engl J Med*. 2006 Feb 16;354(7):767-9; author reply 767-9.

Breast cancer

Demicheli R, Miceli R, Moliterni A, Zambetti M, Hrushesky WJ, Retsky MW, Valagussa P, Bonadonna G. Breast cancer recurrence dynamics following adjuvant CMF is consistent with tumor dormancy and mastectomy-driven acceleration of the metastatic process. *Ann Oncol*. 2005 Sep;16(9):1449-57. Epub 2005 Jun 14.

Locoregional recurrence more important than tumor size

Patients with invasive breast cancer submitted to conservative treatment must be

followed for a long period of time to study locoregional control. In this study, we analysed the outcome and relationships between locoregional recurrence (LRR), distant metastases and survival. A 15-year study, including 470 women with early breast cancer, stage I and II, who underwent breast conservative treatment. Tumour size, nodal status, age, menopausal status, histological grade and LRR were analysed for their ability to predict overall survival, disease-specific survival and distant disease-free survival. RESULTS: With a median follow-up time of 6.6 years (3 months to 19.1 years), there were 19 LRR at their first site of recurrence and 53 distant metastases. Tumour size greater than 2 cm, positive lymph nodes and histological grade III were significantly related to lower overall and distant metastases-free survival. On multivariate analysis, nodal status, histological grade III and LRR (coded as a time-dependent variable) were significantly related to overall, specific and distant metastases-free survival, whereas tumour size had only a borderline effect on specific and distant disease-free survival. Landmark analysis showed that women who presented an LRR within 2 years after surgery had significantly lower distant disease-free survival (hazard ratio [HR]: 8.39; 95% CI 2.56-27.47; $P < 0.001$), specific survival (HR: 8.19; 95% CI 2.45-27.41; $P < 0.001$) and overall survival (HR: 6.02; 95% CI 2.25-16.11; $P < 0.005$). CONCLUSIONS: LRR seems to be a significant predictor of distant metastases and survival, and patients who sustain early LRR tend to display a more aggressive clinical course.

Monteiro Grillo I, Jorge M, Marques Vidal P, Ortiz M, Ravasco P. The effect of locoregional recurrence on survival and distant metastasis after conservative treatment for invasive breast carcinoma. *Clin Oncol (R Coll Radiol)*. 2005 Apr;17(2):111-7.

Does surgery induce angiogenesis in breast cancer?

A significant bimodal relapse hazard pattern has been observed in two independent databases for patients untreated with adjuvant chemotherapy. This implies there is more than one mode of relapse. The earliest and most closely grouped relapses occur 8-10 months after surgery for young women with node-positive disease. Analysis of these data using computer simulation suggested that surgery probably instigated angiogenesis in dormant distant disease in approximately 20% of cases for premenopausal node-positive patients. Surgery-induced angiogenesis accelerates disease by a median of two years and produce 0.11 early deaths per 1000 screened young women in the third year of screening. The predicted timing as well as the magnitude of excess mortality agree with trial data. Surgery-induced angiogenesis could account for the mammography paradox for women aged 40-49 and the bimodal relapse hazard pattern. According to the proposed biology, removing tumors could remove the source of inhibitors of angiogenesis or growth factors could appear in response to surgical wounding.

Retsky M, Demicheli R, Hrushesky WJ. Does surgery induce angiogenesis in breast cancer? Indirect evidence from relapse pattern and mammography paradox. *Int J Surg*. 2005;3(3):179-87. Epub 2005 Sep 12.

Lymph node status more important than tumor size and other grade markers

The purpose of this study was to analyze the prognostic factors affecting local control and survival rates for patients with early breast cancer who received breast conserving treatment (BCT) and to find out the optimal treatment according to their risk factors. METHODS: From October 1994 to December 2001, 605 patients with 611 stage I and II breast cancers received BCT, and the results were analyzed retrospectively. BCT consists of breast conserving surgery and whole breast irradiation. All the patients underwent lumpectomy or quadrantectomy. Axillary lymph node dissection or sentinel lymph node biopsy was performed in 608 cases (99.5%). The radiation dose to the whole breast was 50.4 Gy over 5 weeks with a 1.8 Gy daily fraction and with boost doses of 9-14.4 Gy administered to the tumor bed. Adjuvant chemotherapy was performed in most of the patients with axillary lymph node metastasis or tumors larger than 1 cm. The median follow-up period was 47 months. RESULTS: Local relapse, regional relapse and distant metastasis occurred in 15 (2.5%), 16 (2.6%) and 43 patients (7.1%), respectively. The 5-year overall survival, local-relapse-free survival, distant-metastasis-free survival and disease-free survival rates were 95.3%, 97.2%, 91.3% and 88.5%, respectively. On multivariate analysis, age ($P = 0.02$), number of involved axillary lymph nodes ($P = 0.01$) and nuclear grade ($P = 0.01$) affected the local-relapse-free survival. The factors associated with disease-free survival were the T stage ($P = 0.05$), number of involved axillary lymph nodes ($P = 0.01$) and nuclear grade ($P = 0.001$). Overall survival was associated with the T stage ($P = 0.02$), number of involved axillary lymph nodes ($P = 0.01$) and c-erb B2 overexpression ($P = 0.05$). Patients with more than two factors among (i) age ≤ 35 years, (ii) positive lymph node metastasis and (iii) high nuclear grade showed a poor 5-year local-relapse-free survival rate compared with others ($P = 0.001$). Also, patients with more than two factors among (i) tumor size > 1 cm, (ii) positive lymph node metastasis and (iii) high nuclear grade showed an inferior 5-year disease-free survival rate compared with others ($P = 0.0005$). CONCLUSIONS: The most important prognostic factor affecting local control, disease-free survival and overall survival was axillary lymph node metastasis. The nuclear grade influenced local control and disease relapse. Patients with multiple unfavorable risk factors such as positive axillary lymph nodes, high nuclear grade, young age and large tumor showed poorer local control and disease-free survival than patients without any risk factors, and so more aggressive treatment is required for these patients.

Kim KJ, Huh SJ, Yang JH, Park W, Nam SJ, Kim JH, Lee JH, Kang SS, Lee JE, Kang MK, Park YJ, Nam HR. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. *Jpn J Clin Oncol*. 2005 Mar;35(3):126-33.

Ovarian Cancer: Surgery promotes cancer angiogenesis

Surgical stress has been suggested to facilitate the growth of preexisting micrometastases as well as small residual tumor postoperatively. The purpose of this study was to examine the effects of surgical stress on ovarian cancer growth and to determine underlying mechanisms responsible for increased growth. To mimic the effects of surgery, we did a laparotomy or mastectomy under isoflurane inhalation on athymic nude mice 4 days after i.p. tumor cell injection. Propranolol infusion via Alzet pumps was used to block the

influence of sympathetic nervous system activation by surgical stress. In both HeyA8 and SKOV3ip1 models, the mice in the laparotomy and mastectomy groups had significantly greater tumor weight ($P < 0.05$) and nodules ($P < 0.05$) compared with anesthesia only controls. There was no increase in tumor weight following surgery in the beta-adrenergic receptor-negative RMG-II model. Propranolol completely blocked the effects of surgical stress on tumor growth, indicating a critical role for beta-adrenergic receptor signaling in mediating the effects of surgical stress on tumor growth. In the HeyA8 and SKOV3ip1 models, surgery significantly increased microvessel density (CD31) and vascular endothelial growth factor expression, which were blocked by propranolol treatment. These results indicate that surgical stress could enhance tumor growth and angiogenesis.

Lee JW, Shahzad MM, Lin YG, Armaiz-Pena G, Mangala LS, Han HD, Kim HS, Nam EJ, Jennings NB, Halder J, Nick AM, Stone RL, Lu C, Lutgendorf SK, Cole SW, Lokshin AE, Sood AK. Surgical stress promotes tumor growth in ovarian carcinoma. *Clin Cancer Res.* 2009 Apr 15;15(8):2695-702. Epub 2009 Apr 7.

Kidney cancer: Angiogenesis increases after surgery

The aim of the current study was to assess circulating levels of endogenous endostatin in patients with renal carcinoma and to determine the relationship of these levels to circulating levels of vascular endothelial growth factor (VEGF) and prognosis. **METHODS:** The authors prospectively studied 66 patients (48 male, 18 female; mean age, 50 years) undergoing nephrectomy for renal carcinoma on clinical trials at the National Cancer Institute. Metastases were present in 51 of 66 patients (77%) at the time of nephrectomy. Preoperative and followup serum endostatin and VEGF levels were determined using competitive enzyme immunoassays and compared to a group of 32 age- and gender-matched healthy controls. Associations between circulating endostatin levels and clinicopathologic variables, including survival, were determined. **RESULTS:** Preoperative endostatin levels were higher in renal carcinoma patients than in healthy controls ($P = 0.05$). There was a weak to moderate correlation between pretreatment serum endostatin levels and serum VEGF levels ($r = 0.47$; $P = 0.001$), and levels of both proteins increased significantly following nephrectomy ($P < 0.0001$ and $P < 0.0001$, respectively; $n = 41$). In addition, patients whose endostatin levels increased more than twofold after nephrectomy had significantly poorer prognoses than patients without such an increase ($P = 0.018$). This association was more pronounced when patients without metastases were excluded ($P = 0.0037$). **CONCLUSIONS:** Circulating endostatin levels are elevated in patients with renal carcinoma and correlate with circulating VEGF levels. Endostatin levels increase after nephrectomy, and patients with the greatest increases experience shortened survival times. These findings suggest an association between tumor aggressiveness and the production of endogenous endostatin in patients with renal carcinoma. Published 2002 by the American Cancer Society.

Feldman AL, Alexander HR Jr, Yang JC, Linehan WM, Eyler RA, Miller MS, Steinberg SM, Libutti SK. Prospective analysis of circulating endostatin levels in patients with renal cell carcinoma. *Cancer.* 2002 Oct 15;95(8):1637-43.

Angiogenic growth factor, vascular endothelial growth factor, increases after surgery

Vascular endothelial growth factor (VEGF) is a potent inducer of angiogenesis that is necessary for wound healing and also promotes tumor growth. It is anticipated that plasma levels would increase after major surgery and that such elevations may facilitate tumor growth. This study's purpose was to determine plasma VEGF levels before and early after major open and minimally invasive abdominal surgery. **METHODS::** Colorectal resection for cancer (n = 139) or benign pathology (n = 48) and gastric bypass for morbid obesity (n = 40) were assessed. Similar numbers of open and laparoscopic patients were studied for each indication. Plasma samples were obtained preoperatively and on postoperative days (POD) 1 and 3. VEGF levels were determined via ELISA. The following statistical methods were used: Fisher exact test, unmatched Student t test, Wilcoxon's matched pairs test, and the Mann Whitney U Test with $P < 0.05$ considered significant. **RESULTS::** The mean preoperative VEGF level of the cancer patients was significantly higher than baseline level of benign colon patients. Regardless of indication or surgical method, on POD3, significantly elevated mean VEGF levels were noted for each subgroup. In addition, on POD1, open surgery patients for all 3 indications had significantly elevated VEGF levels; no POD1 differences were noted for the closed surgery patients. At each postoperative time point for each procedure and indication, the open group's VEGF levels were significantly higher than that of the matching laparoscopic group. VEGF elevations correlated with incision length for each indication. **CONCLUSION:** As a group colon cancer patients prior to surgery have significantly higher mean VEGF levels than patients without tumors. Also, both open and closed colorectal resection and gastric bypass are associated with significantly elevated plasma VEGF levels early after surgery. This elevation is significantly greater and occurs earlier in open surgery patients.

Belizon A, Balik E, Feingold DL, Bessler M, Arnell TD, Forde KA, Horst PK, Jain S, Cekic V, Kirman I, Whelan RL. Major abdominal surgery increases plasma levels of vascular endothelial growth factor: open more so than minimally invasive methods. *Ann Surg.* 2006 Nov;244(5):792-8.

Angiogenesis increases (VEGF) after surgery

Angiogenesis is felt to be a factor in the establishment and progression of cancer and cancer metastasis. Vascular endothelial growth factor (VEGF) is one of the most powerful stimulants of tumor angiogenesis identified. VEGF levels can be affected by physiologic stimuli and measured systemically. **METHODS:** Circulating VEGF levels were measured immediately before and after laparoscopic colon surgery in 10 unselected sequential patients with a diagnosis requiring surgical intervention for colon pathology. **RESULTS:** Preoperative VEGF ranged from 31.3 pcg/cc to 187 pcg/cc. Postoperative VEGF ranged from 45 pcg/cc to 2228 pcg/cc. Factors of age, weight, diagnosis, length of cumulative skin incisions, and the receipt of preoperative blood products were considered. Data were compared by t test and regression analysis. Although several patients showed variability, some pronounced, in their pre- and postoperative levels, no 1

factor reached statistical significance as the cause of this variability. Utilizing regression analysis, however, considering only those patients in whom a diagnosis of cancer existed and who received blood products, the length of the incision alone accounted for an R2 change of 0.471. That is, in this subset of patients, incision size alone accounted for almost half of the variability in VEGF. CONCLUSION: The data suggest a possible link between incision size in colon surgery and levels of VEGF. The sample size was insufficient for statistical significance. The study also does not answer whether a systemic release of VEGF at the time of surgery adversely affects the clinical outcome in cases of colon cancer. The data do warrant further investigation with a larger sample size and clinical follow-up.

Fine AP. Minimally invasive surgery may result in lower peak levels of circulating vascular endothelial growth factor. JSL. 2003 Apr-Jun;7(2):147-9.

Open surgery causes in an increase in the metastatic growth factor MMP-9

The authors have previously demonstrated that insulin-like growth factor binding protein-3 (IGFBP-3) is depleted in plasma for 1 to 3 days after major open surgery (OS), but not after laparoscopic surgery (LS). After surgery, IGFBP-3 cleavage occurs rapidly and is likely attributable to altered plasma proteolytic activity. This study aimed to assess plasma proteolysis after both open and closed colorectal resection and, if possible, to identify a protease/protease inhibitor system affected by surgery. METHODS: Plasma from 88 patients with colorectal cancer (stages I-III) who underwent resection was obtained preoperatively (pre-OP) and on postoperative days (POD) 1 to 3. Plasma proteolytic activity was assessed via zymography. On the basis of the results, specific protease and protease inhibitor concentrations were next measured via enzyme-linked immunoassay (ELISA). Statistical analysis was performed using Wilcoxon's test. RESULTS: Early after surgery, zymography showed a predominant band representing a 92-kDa gelatinase corresponding to a proform of matrix metalloproteinase-9 (MMP-9), a protease known to cleave IGFBP-3. In OS patients, the mean concentration of plasma MMP-9 was significantly higher on POD 1 than at pre-OP ($p < 0.003$). On POD 2 and 3, no differences were noted. In the LS group, the mean levels of MMP-9 before and after surgery were comparable. The levels of a natural MMP-9 inhibitor, tissue inhibitor of metalloproteinase-1 (TIMP-1), also were measured. In the OS group, the level of TIMP-1 was significantly higher on POD 1 ($p < 0.0003$) and POD 2 ($p < 0.01$) and 3 ($p < 0.01$) than at pre-OP. In the LS group, a smaller but significant increase in TIMP-1 levels was found between the pre-OP sample and the POD 1 ($p < 0.01$) and POD 2 ($p < 0.01$) samples. No difference was noted on POD 3 ($p = 0.1$). CONCLUSIONS: Open surgery, but not laparoscopic surgery, is accompanied by a short-lived significant increase in MMP-9 levels, which likely accounts for the decrease in IGFBP-3 levels observed after OS. The transitory nature of MMP-9 imbalance may be attributable to the increase in TIMP-1 levels postoperatively.

Kirman I, Jain S, Cekic V, Belizon A, Balik E, Sylla P, Arnell T, Forde KA, Whelan RL. Altered plasma matrix metalloproteinase-9/tissue inhibitor of matrix metalloproteinase-1 concentration during the early postoperative period in patients with

colorectal cancer. Surg Endosc. 2006 Mar;20(3):482-6. Epub 2006 Jan 21. Erratum in: Surg Endosc. 2006 Apr;20(4):706.

Gastric cancer

Angiogenesis and hemostatic activation are important factors in tumor progression and metastasis. Because surgical intervention induces tissue hypoxia and hemostatic activation, we analyzed the effect of gastric surgery on the plasma concentrations of vascular endothelial growth factor (VEGF), soluble P-selectin (sP-selectin), and von Willebrand factor (vWf). **METHODS:** Plasma VEGF, sP-selectin, and vWf concentrations were measured in 14 patients with gastric cancer before operation and on postoperative day 1 (POD 1). Correlations between disease stage and the effect of surgical intervention were analyzed. **RESULTS:** The plasma concentrations of these three factors did not correlate with the disease stage. Plasma levels of sP-selectin did not change after operation (before surgery, 87.6 +/- 34.1 ng/ml; on POD 1, 101.1 +/- 48.1 ng/ml; P = 0.123). Plasma VEGF and vWf concentrations were significantly elevated on POD 1 (VEGF, 33.3 +/- 20.5 pg/ml before surgery and 61.9 +/- 35.6 pg/ml on POD 1; P = 0.0013; vWf, 164 +/- 31.1% before surgery and 211.1 +/- 66.1% on POD 1; P = 0.027). **CONCLUSION:** Because VEGF and vWf are involved in angiogenesis, tumor-platelet adhesion, and tumor-endothelial cell adhesion, surgical intervention influences tumor growth and metastasis.

Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S, Tatsuta M, Kawasaki T, Satomi T. Surgery for gastric cancer increases plasma levels of vascular endothelial growth factor and von Willebrand factor. Gastric Cancer. 2002;5(3):137-41.

Colon cancer (Leukine and surgery increases angiogenesis)

In humans, abdominal surgery is associated with immunosuppression and elevated plasma VEGF levels that might stimulate tumor growth early after surgery. Avoidance of these surgery-related changes and their consequences may be advantageous. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a non-specific immune system up-regulator that has also been associated, experimentally, with increased release of soluble VEGF Receptor 1 (sVEGFR1) which is an endogenous inhibitor of VEGF. This study's purpose was to determine the impact of perioperatively administered recombinant human GM-CSF (rhu-GM-CSF) on both immune function and plasma sVEGFR1 levels in colorectal cancer patients. **METHODS:** This randomized placebo-controlled study included 36 colorectal cancer patients who underwent minimally invasive resection (17 GM-CSF, 19 Placebo). Patients received 7 subcutaneous injections of either rhu-GM-CSF, 125 microg/m², or saline on preoperative days 3, 2 and 1 and on postoperative days (POD) 1, 2, 3 and 4. A number of immune parameters were followed and plasma levels of soluble VEGF Receptor 1 (sVEGFR1) and VEGF were determined. **RESULTS:** The total WBC, neutrophil, eosinophil, and monocyte counts were significantly higher after surgery in the GM-CSF group; no differences were noted for the other immune parameters. In the GM-CSF group, median plasma sVEGFR1 levels were significantly elevated on POD 1 (188.1 pg/ml), and on POD 5 (142.8 pg/ml) when compared to pre-

GMCSF levels (0 pg/ml) (p-value<0.05 for all comparisons). In the placebo group, the POD5 median sVEGFR1 level (116.3 pg/ml) was elevated and of borderline significance (p=0.05) vs the pre-treatment result (0 pg/ml). Of note, both groups had significantly elevated median plasma VEGF levels on POD 5 (Control 435.7 pg/ml; GMCSF 385.3 pg/ml) when compared to their preoperative results (Control 183.3 pg/ml, p=0.0013; GMCSF 171.5 pg/ml, p=0.0055). CONCLUSIONS: Perioperative GMCSF was not associated with an immune function benefit in this study, however, such treatment leads to increased plasma sVEGFR1 levels. Colorectal resection, with or without GMCSF, was also associated with increased VEGF levels postoperatively. Increased plasma levels of sVEGFR1 after surgery might limit the pro-angiogenic tumor stimulatory effects of VEGF. Further study of GMCSF's impact on angiogenesis appears warranted.

Kirman I, Belizon A, Balik E, Feingold D, Arnell T, Horst P, Kumara S, Cekic V, Jain S, Nasar A, Whelan RL. Perioperative sargramostim (recombinant human GM-CSF) induces an increase in the level of soluble VEGFR1 in colon cancer patients undergoing minimally invasive surgery. *Eur J Surg Oncol.* 2007 Dec;33(10):1169-76. Epub 2007 May 18

Skip Dissection for Patients with Advanced Neck Cancer Who Respond to Chemoradiation

Patients with advanced neck cancer who experience a clinical complete response to chemoradiation will likely not require dissection, researchers report. Presenting here at the 2007 Multidisciplinary Head and Neck Cancer Symposium in Rancho Mirage, California, experts showed that patients experienced long-term control of 85% or greater without surgery.

"This is an issue that has been debated pretty intensely in recent years," lead author Ramesh Rengan, MD, from the University of Pennsylvania, in Philadelphia, told Medscape during an interview. "But there has been increasing concern that neck dissection after a complete response to chemoradiation is needlessly adding toxicity, and our results appear to confirm that most of these patients would not benefit from this invasive procedure."

Rengan, Ramesh, Skip Dissection for Patients with Advanced Neck Cancer Who Respond to Chemoradiation, 2007 Multidisciplinary Head and Neck Cancer Symposium: Abstract 8. Presented January 19, 2007, Medscape Medical News 2007. © 2007 Medscape

Glioblastoma: Standard of Care of Surgery, Radiation, and Chemotherapy Promotes Brain Tumor Cells

The medical standard of care -- comprised of surgery, radiation and chemotherapy -- for the most common form of brain cancer triggers a number of biological responses that may actually feed the energy metabolism that supports the disease, according to Boston College researchers writing in the journal *Lancet Oncology*.

The deadly glioblastoma multiforme leaves the average patient a median survival of about a year from diagnosis. Just three percent of patients afflicted with the fast-moving brain cancer survive 36 months. The standard of care for the treatment of the disease has not changed markedly since it was established 50 years ago.

But the effects of surgery, radiation and chemotherapy produce a range of biochemical responses in the brain that can fuel tumor cell survival at the same time doctors are attempting to eradicate the disease, according to Boston College Professor of Biology Thomas Seyfried, whose lab has researched ways to deny energy to cancer cells.

"All tumors, regardless of where they are located, require two major fuels for survival: glucose and glutamine," said Seyfried, a specialist in lipid biochemistry. "As long as tumor cells have access to these energy molecules, they will survive. If you give them a lot of these molecules, they will survive even better."

The three components of cerebral cancer care may play a role in providing tumor cells with the metabolic fuels they need to survive. While these treatments reduce tumor growth over the short term, radiation and certain chemotherapies could actually contribute to the high recurrence of these deadly tumors.

A growing body of research over the past decade, according to Seyfried, now shows the processes of radiation and chemotherapy can serve to increase the supply of glucose and glutamine, leading to conditions favorable to tumor cell survival and growth.

Furthermore, **infection-fighting tumor-associated macrophages and monocytes (TAMs) that flood the brain in an effort to battle tumor cells can indirectly support tumor growth through the release of agents that lead to inflammation and the growth of blood vessels.**

"What develops then is an escalating situation of biological chaos, where the intrinsic properties of TAMs to heal wounds increase the capacity of brain tumor cells to proliferate, invade, and self-renew," writes Seyfried and his co-authors, researchers Laura M. Shelton and Purna Mukherjee.

Seyfried says this "perfect storm" of side-effects from the standard of care for glioblastoma should invite a broader discussion among researchers for potential alternative therapies. Through his past research, Seyfried has detailed the benefits of non-toxic metabolic therapies involving ketogenic diets that effectively restrict glucose-based fuels to brain tumors. By regulating glucose availability while simultaneously elevating fat-derived ketone bodies, which brain tumors cannot actively use for growth or survival, the ketogenic diet has been shown to control epileptic seizures, but there have been no human trials to test its therapeutic efficacy against brain cancer.

Seyfried et al. **Does the existing standard of care increase glioblastoma energy metabolism?** *The Lancet Oncology*, 2010; DOI: 10.1016/S1470-2045(10)70166-2 Boston College (2010, July 18). Does the existing standard of care supply energy sources to brain tumor cells?. *ScienceDaily*. Retrieved July 22, 2010, from <http://www.sciencedaily.com/releases/2010/07/100714112834.htm>

Conclusion

As we continue to delve more deeply into the truths uncovered through the exploration of cancer and its unquestionable, metaphoric roots in our own process of uncontrolled growth, we will find that systemic terrain change is the only way to achieve health and harmony. As we continue to shape our external world environment with greed and non-compassionate action towards the flora and fauna of our island home, these actions will be reflected in our internal environment. The wholistic approach to the disabling of cancerous growth must take into consideration the human process of growth and development. As long as we strive to take more for ourselves than we are willing to give back, we will always be in disharmony.

Removing a tumor through resection is an aggressive and invasive action, and one that should be carefully considered when facing an already hostile, unstable internal environment. As seen herein, the evidence is beginning to find its way into the forefront of modern research that surgery is not a curative treatment for systemic cancer. Until the allopathic, emergency medicine model is aware of the detriments of its emergency treatment approaches for addressing chronic conditions, we will be unsuccessful at treating and curing our most deadly diseases. Surgery has its place in cancer treatment, but it needs to be used wisely and with a greater understanding of the cost-to-benefit ratio achieved by it; also timing is everything. I believe it should be preserved a later treatment rather than as a first line treatment, as it is presently used unless it is an emergency and must be performed to save a person's life. I also believe Immunonutrition and botanical medicine needs to be given weeks prior, or at least one week before surgery.

The significance of perioperative immunonutrition

Perioperative immunonutrition is aiming at modulating altered immunological and metabolic functions in the context of major surgery. It is defined as the supplementation of constitutionally essential substrates such as glutamine, arginine, omega-3-fatty acids or nucleotides. The application of such formula is recommended for patients undergoing major abdominal-surgical procedures and tumour surgery in the head neck area. The substitution should be given 5-7 days before and after the intervention.

Schreiter D, Rabald S, Bercker S, Kaisers UX. The significance of perioperative immunonutrition, *Laryngorhinootologie*. 2010 Feb;89(2):103-13. Epub 2010 Feb 12.

Cancer-promoting effects of radiotherapy

Radiation therapy has been in use as a cancer treatment for more than a century, with its earliest roots traced from the discovery of x-rays in 1895 by Wilhelm Röntgen. Two-thirds of all cancer patients will be treated with radiotherapy at some point in their life. (Hogle WP. The state of the art in radiation therapy. *Semin Oncol Nurs*. 2006;22:212–20.) Ionizing radiation causes DNA damage through induction of breaks in one or both of DNA strands. Since cancer cells display deregulated cell cycle control and increased proliferation they are more vulnerable to irradiation than normal cells which usually are able to repair the DNA damage or to induce cell death in those cells in which DNA

damage cannot be repaired. The effect of radiation on cancer cell or normal cell does not always take place immediately after treatment. Some of the cells will stay unchanged for weeks or months after treatment. This is due to the fact that radiation damaged cells can stay alive as long as all DNA is present. However, proper cell division is impossible after DNA is damaged. These radiation damaged cells can initiate a second cancer somewhere else in the body.

Numerous studies confirmed that radiotherapy increases the risk of second malignancies. Radiation-induced bone cancers and soft tissue sarcomas have been observed in long-term survivors of hereditary retinoblastoma. Most deaths from these secondary malignancies occurred within 30 years after retinoblastoma diagnosis. (Marees T, van Leeuwen FE, de Boer MR, et al. Cancer mortality in long-term survivors of retinoblastoma. *Eur J Cancer*. 2009;45:3245–53.) In patients with Hodgkin's lymphoma, causes other than primary disease contribute most to excess mortality 10 years after radiotherapy. Solid tumors, especially from the digestive and respiratory tract, contribute most to this excess mortality, followed by cardiovascular disease. (Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol*. 2003;21:3431–9.) Statistically significantly increased risks of solid cancers (lung, colon, bladder, pancreas, pleura and esophagus) are observed among long-term survivors of testicular cancer treated with radiotherapy alone. (Travis LB, Fosså SD, Schonfeld SJ, et al. Second cancers among 40, 576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*. 2005;97:1354–65.) Men who receive radiotherapy for localized prostate cancer have an increased risk of bladder cancer compared to patients undergoing radical prostatectomy and compared to the general population. The risk of rectal cancer is increased in patients who receive external beam radiotherapy compared to radical prostatectomy. (Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. *J Urol*. 2008;180:2005–9.)

Dainius Characiejus & Jasmina Hodzic & John J. L. Jacobs, "First do no harm" and the importance of prediction in oncology, *EPMA Journal* (2010) 1:369–375