

## Cancer Surgery

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Surgery poses many risks to a cancer patient. The known side effects associated with the surgical removal of tumors include anesthesia complications, infections, and immune suppression.

A surgery side effect of concern to cancer patients is that the removal of the primary tumor may directly stimulate cancer spread (the propagation of metastatic lesions). Metastatic tumors require the formation of new tumor blood vessels (called angiogenesis) to grow.

Once the primary tumor has been surgically removed, the amount of endostatin and angiostatin to control new tumor blood vessel growth is drastically reduced, and metastasized lesions begin proliferating out of control. If the immune depression that surgery induces is factored in, the failure of surgery to meaningfully prolong the life of cancer patients becomes quite understandable. Surgery reduces growth control factors (endostatin and angiostatin) while simultaneously weakening the immune surveillance that might be keeping metastatic lesions under some degree of control (Oliver et al. 1996).

Cancer has long baffled medical science. Until recently, scientists did not fully understand why the disease so often begins rapidly spreading throughout the body after surgery. This protocol identifies previously unknown factors involved in the long-term failure of cancer surgeries. The educated patient now has access to drugs to facilitate systemic control of cancer rather than to promote metastasis.

Even more exciting is the news that drugs such as endostatin and angiostatin are in clinical trials. If the FDA approves these drugs, the surgical removal of a large primary tumor might actually "cure" many more cancer patients. In the meantime, there are other anti - angiogenesis drugs that may help prevent the rapid growth of metastatic lesions after the primary tumor is removed.

### HOW TUMORS GROW

Almost every tissue in the body derives blood from the thinner-than-a-hair capillaries that lace our tissues. Through capillaries, nutrients, oxygen, and various signaling molecules diffuse into cells. These mechanisms maintain health, fight disease, and allow the body to flourish and grow.

Tumors start out without a vascular circulation. In the early stages of tumor development, they are limited to nutrients that can diffuse from the nearest capillaries. Then, tumors begin to stimulate healthy tissue to make thousands of new blood vessels to supply the cancerous growth--a process called angiogenesis. Without this ability to nourish itself and grow, a tumor cannot enlarge. If the blood supply can be reduced or cut off, the tumor will shrink or die.

### REMOVING ONE TUMOR MAY STIMULATE THE GROWTH OF MANY MORE

Recurrence is the point when cancer cells from the primary tumor are detected following the primary treatment for the cancer.

Ipsilateral breast tumor recurrence following conservative surgery and radiation for early stage invasive cancer occurs in approximately 15% of all patients at 10 years and is reduced with surgical excisions which achieve negative margins (Fowble 1999). Local recurrence continues to be a major problem following surgical treatment for rectal cancer, because of the frequency with which it occurs (varying from 4% to 51%), its impact on quality of life, the fact that treatment is rarely successful (McLeod 1997), and the proposed ways of reducing this remain controversial ( McCall et al. 1995).

All patients undergoing laparoscopic surgery for malignancies should have careful follow-up with special attention to the port sites, as port-site metastasis after laparoscopic lymphadenectomy is a phenomenon that occurs following this type of cancer surgery ( Tjalma et al. 2001).

Several drugs--including interferons, steroids, and certain hormonal agents--have been developed to stop or slow angiogenesis. In fact, at least 11 anti-angiogenic drugs are in clinical trials, and three have proved effective enough to make it to the final phase.

Some of the drugs, like endostatin, are derived from natural proteins, while others are based on smaller molecules. Ironically, one promising drug in clinical trials is thalidomide, which once was sold as a sedative that caused notorious birth defects.

Another drug, 2-methoxyestradiol (2-ME), is a natural estrogen metabolite believed to be an inhibitor of angiogenesis and also an anti - tumor agent.

In addition, researchers are investigating a drug called Col-3 and are negotiating with several biotechnology companies to examine other anticancer compounds.

Of all the anti - angiogenic drugs, endostatin and angiostatin appear to hold the greatest potential for saving lives. These drugs are nontoxic and have shown efficacy against every type of cancer tested. These drugs suppressed metastatic tumor growth rates by 90% (Hajitou et al. 2002). Another study showed primary tumors regressing to become dormant microscopic lesions (O'Reilly et al. 1997).

Based on this new information, angiostatin and endostatin may greatly increase the number of cancer patients who become disease-free after surgery.

## HOW TO ENTER CLINICAL TRIALS

Endostatin was the first endogenous angiogenesis inhibitor to enter into clinical trials. Endostatin given to 21 advanced solid tumor patients daily as a 1-hour intravenous infusion (for 28 days) was well - tolerated (Thomas et al 2003).

The safety and efficacy of recombinant human Angiostatin protein administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with non-small-cell lung cancer is currently being investigated in a clinical trial:  
<http://clinicaltrials.gov/ct/search?term=angiostatin>

For more information about cancer clinical trials call the Cancer Information Service, (800) 4-CANCER.

Physicians may request information about trials from the PDQ Search Service by calling (800) 345-3300, faxing (800) 380-1575, or e-mailing [pdqsearch@icicc.nci.nih.gov](mailto:pdqsearch@icicc.nci.nih.gov).

There are many anti - angiogenesis drugs in clinical studies. In some cases, the FDA may allow an unapproved drug to be released before it is officially approved. Here are some of the anti - angiogenesis drugs being tested and the sponsoring companies:

Drug	Phase	Sponsor
TNP-40	II	TAP Pharmaceuticals Inc., Deerfield, WI
Squalimine	II	Genera Pharmaceuticals Inc., Plymouth Meeting, PA
Vitaxin	I	Ixsys Inc., San Diego , CA
Thalidomide	II	Extremed Inc., Rockville, MD
RhuMab, VEGF	II	Genentech, Inc., South San Fransisco, CA
SU5416	II	Sugen Inc., Redwood City, CA
Marimastat	III	British Biotech Inc., Annapolis, MD
Bay 12-9566	III	Bayer Corp., West Haven, CT
AG3340	III	Agouron Pharmaceuticals Inc., La Jolla, CA
Col-3	I	CollaGenex Pharmaceuticals, Newton, PA
CM101	I	Carbomed Brentwood, TN

## THE FIRST ANTI-ANGIOGENESIS DRUG IS APPROVED

After many years of study, the drug Avastatin® has been approved by the FDA to treat colon cancer. It may also be effective against other cancers.

In a well-performed Phase III trial, Avastatin® was shown impressively to prolong survival for patients with metastatic colorectal cancer that could not be removed by surgery (unresectable). ( O'Neil et al. 2003).

Avastatin® (bevacizumab) is an anti - angiogenesis drug, used in molecular targeted therapy to stop tumors from making new blood vessels. It works by keeping VEGF (vascular endothelial growth factor) from initiating the growth of new blood vessels. Without new blood vessels, tumor growth is inhibited. Avastatin® is now being studied for the treatment of many different cancers.

Patients with newly diagnosed metastatic colon cancer who received Avastatin® along with a chemotherapy combination (known as IFL) had substantially longer overall survival times than patients who received the chemotherapy but with a placebo instead of bevacizumab.

A randomized Phase III trial to compare the effectiveness of two combination chemotherapy regimens with or without bevacizumab in treating patients who have locally advanced, metastatic, or recurrent colorectal cancer is underway via the National Institutes of Health (NIH). A Phase I trial to study the effectiveness of bevacizumab combined with fluorouracil and external-beam radiation therapy in treating patients who have stage II or stage III rectal cancer is also ongoing via the NIH.

## PROTECTING AGAINST SURGERY-INDUCED IMMUNE SUPPRESSION

Human and animal studies demonstrate that surgery suppresses immune function. In fact, surgical stress directly reduces natural killer (NK) cell activity, and other immune factors (Hansbrough et al. 1984; Pollock et al. 1991; Udelsman et al. 1991). NK cells have a fundamental role in destroying cancer cells and are involved in inhibiting metastasis (Herberman et al. 1981; Gorelik et al. 1982; Hanna 1985; Wiltout et al. 1985; Ben-Eliyahu et al. 1999).

A regrettable consequence of surgery is suppression of vital NK cell activity, thereby making the patient more susceptible to developing metastatic lesions. In the animal model, surgery-induced immune suppression has been linked to tumor metastasis to the lung (Page et al. 1994 a ; 1994b; Ben-Eliyahu et al. 1999). Human studies demonstrate that those with low NK cell activity have an increased risk of metastatic lesions (Levy et al. 1985; Schantz et al. 1987; Tartter et al. 1987; Fujisawa et al. 1997; Koda et al. 1997).

Despite the known immune-suppressing effects of surgery, removal of the primary tumor is often mandatory in order to provide the cancer patient with an opportunity for a cure. What oncologists have overlooked are the many adjuvant therapies that can promote immune function, specifically natural killer cell activity.

In the *Cancer Adjuvant Therapy protocol* , natural approaches of boosting immune function are discussed. The cancer patient contemplating surgery may consider supplementation with melatonin, lactoferrin, echinacea, and a special preparation called "MGN-3" for the purpose of enhancing NK cell activity (Ghoneum et al. 2000; Currier et al. 2001; Huang et al. 2002; Tsuda et al. 2002). While these therapies are by no means a cure for cancer, they do provide patients with an opportunity to mitigate the immune suppression associated with surgical procedures.

## AVOID ANALGESIC DRUGS THAT PROMOTE METASTASIS

After cancer surgery, the patient often experiences pain and requests an analgesic drug for immediate relief. The drug of choice is often morphine or an other opiates. The problem with these drugs is that they impair immune function, specifically NK activity, lymphocyte-macrophage production, and other key immune cytokines. It is during this postsurgical period that healthy immune function is required to kill cancer cells that have escaped from the primary tumor and are seeking to set up metastatic colonies.

Unfortunately, morphine is often prescribed to post - surgery cancer patients at the very time when optimal immune function is most needed to eradicate residual tumor cells. Instead of accepting morphine and other opiates, ask your doctor for an analgesic drug called "tramadol." Unlike morphine, tramadol does not suppress immune function. On the contrary, tramadol has been shown to stimulate NK activity in animals and humans. In a study on rats, tramadol was able to block the enhancement of lung metastasis induced by surgery, whereas morphine did not produce this beneficial effect (Gaspani et al. 2002).

Because tramadol produces a good analgesic effect combined with immune-enhancing properties, it may be the drug of choice for controlling postoperative pain in cancer patients.

Morphine has other deleterious effects on the cancer patient. In addition to impairing immune function, morphine stimulates angiogenesis (new blood vessel growth that feeds rapidly dividing tumors), activates a tumor cell survival signal, and inhibits apoptosis (programmed cell death) of cancer cells (Gupta K. et al. 2002). All of these negative effects occur at morphine doses typically given to cancer patients.

In one study, morphine was specifically shown to promote the growth of a human breast tumor implanted into an animal. Interestingly, an analgesic-antagonist drug called naloxone inhibited tumor growth (Maneckjee et al. 1990). Based on these findings, it was suggested that the pro - angiogenesis effect of opioids (morphine) might be detrimental to cancer patients (Gupta et al. 2002).

These studies help explain why cancer patients given morphine often succumb quickly. This may be desirable for terminal cancer patients in the hospice setting. For cancer patients undergoing potentially curative surgery, it appears imperative that they refuse morphine and any other opiate-type analgesic. They should instead request the drug tramadol to alleviate postoperative pain.

## SUMMARY

For many forms of cancer the surgical removal of the primary tumor is crucial if long-term remission is to occur. Anti-angiogenesis drugs given prior to cancer surgery may improve the chances of a long-term remission. These drugs would also theoretically be of value in the post - operative setting, though they may slow the rate of healing.

Surgery suppresses important immune functions needed to kill metastatic tumor cells. The patient should consider taking supplements that enhance immune function, such as melatonin, lactoferrin, and garlic, before and after surgery.

Avoiding analgesic drugs, such as morphine and other opiates, helps prevent immune suppression and the development of tumor angiogenesis. For pain suppression in the postoperative environment, the drug tramadol should be requested in lieu of morphine or other opiates.

For cancer patients undergoing surgery, or any other type of cancer therapy, it is important to review the information that appears in the *Cancer Adjuvant Treatment protocol*. Therapies discussed in this protocol can help protect against surgically induced immune suppression, thus improving the odds of long-term survival.

## PRODUCT AVAILABILITY

Melatonin, lactoferrin, echinacea, and MGN-3 are available by phoning (800) 544-4440 or by ordering online.

## STAYING INFORMED

The information published in this protocol is only as current as the day the manuscript was sent to the printer. This protocol raises many issues that are subject to change as new data emerge. Furthermore, cancer is still a disease with unacceptably high mortality rates, and none of our suggested regimens can guarantee a cure.

The Life Extension Foundation is constantly uncovering information to provide to cancer patients. A special website has been established for the purpose of updating patients on new findings that directly pertain to the published cancer protocols. Whenever Life Extension discovers information that may benefit cancer patients it will be posted on the website [www.lefcancer.org](http://www.lefcancer.org).

Before utilizing the cancer protocols in this book, we suggest that you check [www.lefcancer.org](http://www.lefcancer.org) to see if any substantive changes have been made to the recommendations described in this protocol. Based on the sheer number of newly published findings, there could be significant alterations to the information you have just read.

Alternatively, call 1-800-226-2370 and ask a Health Advisor if your topic of interest has been updated on the website - [www.lefcancer.org](http://www.lefcancer.org).

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