

THE GONZALEZ THERAPY AND CANCER: A COLLECTION OF CASE REPORTS

Nicholas J. Gonzalez, MD; Linda L. Isaacs, MD

Nicholas J. Gonzalez, MD, and Linda L. Isaacs, MD, run a private practice in New York City, where they research treatments for a variety of diseases, particularly advanced cancer, and see patients.

In our practice, we offer an aggressive nutritional program for treatment of advanced cancer and a variety of other serious illnesses, ranging from chronic fatigue to multiple sclerosis. Whatever the underlying problem, our therapy involves 3 basic components: individualized diets, individualized supplement protocols, and intensive detoxification. The diets we prescribe can range from vegetarian raw foods to an Atkins-type red meat approach. The supplement programs are equally as varied, involving vitamins, minerals, and trace elements in various forms and various doses, as well as glandular and enzyme products, each chosen to meet a particular need in each patient. The detoxification routines, often the most misunderstood component of our therapy, consist of coffee enemas and a variety of other techniques that actually have been adapted from the orthodox medical literature. We believe these procedures help the body neutralize and excrete the multitude of waste products produced during routine metabolism and, in the case of our cancer patients, resulting from tumor lysis.

We are perhaps best known for our work with advanced cancer. For patients suffering malignancy, we rely on large doses, spread throughout the day, of orally ingested pancreatic enzymes derived from a pig source. Though we believe the diets, vitamins, minerals, and trace elements help improve tissue and organ efficiency, in our therapy, it is the pancreatic enzymes that target and kill cancer cells.

HISTORY OF ENZYME TREATMENT

The enzyme treatment of cancer has a long history, beginning with the work of Dr John Beard, a professor at the University of Edinburgh who in 1902 first proposed that the pancreatic proteolytic enzyme trypsin might represent a powerful anti-cancer tool. Beard, an embryologist, detoured into cancer research as a result of his studies of the mammalian placenta and its similarity to malignant tumors.

Beard was the first to report that in many respects, the placenta in its early form behaves like a tumor. It begins growing as a very undifferentiated offshoot from the primitive embryo, then

quickly invades the mother's uterus, much as a tumor infiltrates host tissue in any organ. Initially, the cells of the placenta proliferate almost without control, as tumors were known to do even in Beard's day, and it quite efficiently produces a dense blood supply—a requirement for any rapidly growing malignancy, as angiogenesis research today has made clear.

As normal development proceeds, however, at some predetermined point, the placenta transforms from a highly invasive, rapidly growing, blood vessel-producing, tumor-like tissue, to the non-invasive, non-proliferating mature organ. The only difference between the placenta and a malignant growth, Beard claimed, is that the placenta knows when to stop growing, and tumors don't.

Beard concluded that the key to the change lay in the embryonic pancreas. As witnessed in every species he studied, the day the placenta stops its cancer-like invasion of the mother is the very day the embryonic pancreas becomes active and begins pouring out enzymes.

Even in Beard's day, more than 100 years ago, the main categories of pancreatic enzymes had already been identified—the proteolytic, or protein-digesting component; the lipases, which hydrolyze triglycerides, and the amylases, responsible for cleaving complex carbohydrates into simple, easily usable sugars. Physiologists of the time thought all 3 groups were active only in the duodenum, where the enzymes continue the breakdown of food arriving from the stomach. But Beard effectively provided the data to illustrate that above and beyond this function, trypsin, the main proteolytic enzyme, served to control placental growth and prevent the tissue from invading beyond the uterus, as a true cancer might.

Beard proposed that because the early placenta behaves much as a tumor does, because under the microscope its cells even look like undifferentiated, primitive neoplastic cells, and because pancreatic enzymes forcefully regulate its growth and development, these very same enzymes could be—in fact, must be—the body's main defense against cancer and would be useful as a cancer *treatment*.

Beard first tested his thesis in the one animal tumor model available at the time, the Jensen's mouse sarcoma. He injected an extract of trypsin into mice growing such cancers, and the tumors regressed.¹ Subsequently, during the first decade of the 20th century, a number of physicians interested in Beard's hypothesis began, under his direction, to use injectable pancreatic enzymes to treat their human cancer patients. The successes were published in

the major medical journals of the day, including *JAMA*² and the *British Medical Journal*.³

The enzyme thesis, and the supporting animal and laboratory data, provoked an angry backlash against Beard and his followers. He was vilified in editorials in medical journals, mocked in the newspapers, and belittled at scientific conventions. But Beard fought back in articles and letters to the editor, and in 1911, he published *The Enzyme Treatment of Cancer*,⁴ a monograph outlining his decades of research and its promising and compelling results. But interest in Beard's thesis gradually petered out, and when he died in 1924, he died frustrated, angry, and ignored, his therapy already considered no more than a historical oddity.

After Beard's death, other physicians and scientists discovered his work and kept the idea alive. During the 1920s and 1930s, a St Louis physician, Dr F. L. Morse, reported that he had successfully treated a number of advanced cancer patients with pancreatic enzymes. When he presented his findings to the St Louis Medical Society in 1934—a proceeding published in the *Weekly Bulletin of the St Louis Medical Society*⁵—his colleagues attacked him.

During the 1960s, the eccentric dentist Dr William Kelley rediscovered Beard's work and developed his own variation of enzyme treatment. In addition to large doses of orally ingested pancreatic enzymes, Kelley's program included individualized diets, supplement protocols, and detoxification routines. Kelley came to fame at a time of great repression organized against alternative medicine. He was at particular risk because as a dentist, he was not legally entitled to treat cancer in the first place. He was attacked in the press, vilified as a "quack," and investigated by numerous government agencies. He was thrown in jail as a public menace, had his dental license revoked for 5 years for practicing medicine, spent his earnings defending himself against government assaults, and saw his family life fall apart. But, like Beard, he never relented, and his successes created an extraordinary word-of-mouth network that brought an endless stream of patients to his practice.

DR GONZALEZ'S RESEARCH BEGINS

I (NJG) met Dr Kelley during the summer after my second year of medical school. I had as a mentor at Cornell Medical College the late Robert A. Good, MD, PhD, who encouraged a review of Kelley's cases. Dr Good, then President of the Sloan-Kettering Research Institute, was the most published author in the history of the biomedical scientists, the "father of immunology," as *The New York Times* described him, and the man who performed the first bone marrow transplant in history.

Under Dr Good's direction, I began a student project evaluating Dr Kelley's patients, his methods, and his successes and failures. I quickly found evidence of what appeared to be patient after patient with appropriately diagnosed, biopsy-proven advanced and sometimes terminal cancer, who were alive 5, even 10 years after first beginning enzyme therapy. What began as a mere student investigation evolved into a full-fledged research project, completed while I was a fellow in Dr Good's practice, which ended up at All Children's Hospital in Florida.

I eventually interviewed and evaluated more than 1,000 of Kelley's patients and concentrated on a group of 455. From this population, I wrote up in detail 50 cases, representing 26 different types of cancer. Even today, 20 years later, when I review the cases, I am impressed by Kelley's achievement. By 1986, I had put the results of my 5-year investigation into monograph form and intended to publish them. To my disappointment and surprise, I could not get the book published either in its entirety as a monograph or as a summary journal article. The responses from editors ran the gamut from disbelief and accusations of fraud to fear that the book would generate so much controversy that publishing careers might be ruined.

Our inability to get the study published had a damaging effect on Dr Kelley. It appeared that his work would never be accepted for what he believed it was—a promising answer to a deadly disease. In 1986, he closed down his office, and eventually disappeared from sight. After 1987, I never spoke to him again. Determined to keep the enzyme therapy alive, I left Dr Good's group when I finished my fellowship and returned to New York in 1987. I began seeing patients, always with the hope of obtaining proper research support from the academic world.

In July of 1993, the National Cancer Institute (NCI) invited me to present case reports from my practice, detailing patients with appropriately diagnosed poor-prognosis cancer who had enjoyed tumor regression or unusual survival while following my therapy. Dr Isaacs and I put together 25 cases for the session, which was attended by a large group of NCI scientists and lasted 3 hours. After the meeting, I was asked to pursue as a next step a pilot study evaluating my approach in 10 patients diagnosed with advanced adenocarcinoma of the pancreas. In such phase II studies, as they are technically called, a promising new therapy is administered to patients with an aggressive cancer for which there is no effective standard treatment. A pilot study involves no control group, but can still give important information about a treatment. Because inoperable pancreatic cancer has such a grim prognosis, with an average survival in the range of 3-6 months, the associate director who chaired the meeting suggested that if I could get 3 patients to live a year, that would be a significant success.

We were fortunate to get funding for the study from Nestle, the giant international food conglomerate. The then-vice president in charge of research at Nestle, Dr Pierre Guesry, who had previously been medical director of the Pasteur Institute in Paris, had learned of my work and become a supporter.

We finished the study and published the results in June 1999, in the peer-reviewed research journal *Nutrition and Cancer*.⁶ We had eventually included 11 subjects, adding a patient when one dropped out. Of the 11, all had biopsy-proven, inoperable disease, 8 of the 11 had stage IV, most had been very sick before consulting with us. All of the patients were approved by a consulting oncologist and the late Dr Ernst Wynder, one of the premier cancer epidemiologists of the 20th century. Of the 11, 9 lived more than 1 year, 5 lived more than 2 years, 4 lived more than 3 years, and 2 lived more than 4 years. As a point of reference, in the clinical trial

of gemcitabine (Gemzar), the latest drug approved for the disease, of 126 patients treated with chemotherapy, not 1 lived longer than 19 months.⁷ Ours were results that previously had not been reported for the disease.

Shortly after the article was published, the NCI approved funding for a large-scale, phase III clinical trial, again testing our enzyme approach in patients with advanced pancreatic cancer, but this time against a control group that would receive the best available chemotherapy. Eventually, the US Food and Drug Administration (FDA) approved the protocol and the National Center for Complementary and Alternative Medicine (NCCAM) offered to provide the required funding. Columbia University, under the chief of oncology at the time, and the chief of surgical oncology, became the supervising institution in New York, where the study would be conducted. Unfortunately, 7 years later, the project remains unfinished, beset by bureaucratic difficulties.

Nonetheless, as the NCI study bogged down, Dr Guesry at Nestle provided funding for studies to test the enzyme treatment in animal models, to provide supportive data to the human clinical trials. A group at the Eppley Cancer Institute of the University of Nebraska known for their investigations into the molecular biology of pancreatic cancer agreed to take on the challenge. Dr Parviz Pour, the supervisor of the animal work at Nebraska, has developed mouse models of pancreatic cancer that are used to test promising new treatments against the disease.

In May 2004, the results of the experiments were published in the peer-reviewed journal *Pancreas*.⁸ In these studies, the researchers evaluated the effect of our enzymes in nude mice injected with human pancreatic cancer cells of a particularly virulent strain. These mice lack a functional immune system, so normally the tumors grow very rapidly and kill quickly. In the first study, which measured survival, the mice were divided into 2 groups, 1 receiving our enzymes, the other given no therapy. The animals treated with our enzymes survived significantly longer than the untreated control group and appeared to be healthy and happy well into the study, in sharp contrast to the controls, which were listless, inactive, bloated, and quite ill.

In a second experiment, again the mice were divided into 2 groups, 1 administered our enzymes, the other untreated. This time, animals were periodically sacrificed and evaluated for tumor growth. The enzymes clearly reduced the proliferation of the tumors, which in the treated mice remained small and very localized. In the controls, tumors were considerably larger and more invasive.

These results are particularly significant because we have never used the enzymes to treat animals before and decided to start at the dose per kilogram that we would normally use in humans. Inbred laboratory mice, however, metabolize most drugs far differently than we do, and normally doses much higher than what would be given humans must be administered to get an effect. Furthermore, the experiments evaluated only the enzyme component of the treatment, not the additional vitamins, minerals, trace elements, and nutritious food we prescribe for our human patients. The animal chow also contained a fair amount of

soy, which, however aggressively it may be pushed as a beneficial food, contains one of the most potent natural trypsin inhibitors.

MEASURES OF SUCCESS

Conventional medical journals often publish case reports—descriptions of individual patients whose disease might have taken an unusual course in response to some new treatment. Such “anecdotal evidence” contrasts with a controlled clinical trial, in which different treatments are given to large groups of patients with a particular illness, and the results compared. Some scientists contend that only such rigorous exercises, ideally pursued under the most stringent rules and regulations, can “prove” that a new treatment for a disease has any value. They often argue that case reports, though perhaps interesting or entertaining, have little scientific merit.

Dr Good always insisted that case reports, if properly written and carefully documented, can teach us much about the potential of a new approach. When I first began to evaluate Kelley’s records, Good said that if I could find even 1 patient with appropriately diagnosed, biopsy-proven metastatic pancreatic adenocarcinoma who had lived 5 years under Kelley’s care he would be impressed, as no one else in medicine to his knowledge had such a case.

In terms of cancer, a case report, to have value, must meet certain basic criteria. First, the diagnosis must be confirmed by biopsy, and the stage by appropriate radiographic studies or surgical procedures. Then, the unusual response to treatment must be carefully defined, explained, and documented. The endpoints of most importance for cancer case reports include objective evidence of improvement in the underlying disease, or unusual prolonged survival.

For patients with the typical solid epithelial tumors, disease regression can be verified by serial radiographic studies, such as positron emission tomography (PET) or computed tomography (CT) scans. For blood cell malignancies such as leukemia or myeloma, normalization of blood parameters, such as white count or blood protein, might be the marker followed over time.

Survival, if particularly unusual, can be a valid endpoint with or without evidence of disease regression. If this is the chosen criterion, the patient in question must have lived far beyond the accepted medians and means for the disease. Such information on expected survival can be culled from a number of sources, both governmental and private, so comparisons can be made. The Surveillance, Epidemiology, and End Results (SEER) Program and American Cancer Society websites, for example, provide survival statistics, including medians and means, for many cancers. However, no precise definition of “significantly” prolonged survival really exists, so it becomes more of a judgment call in each case. When I first presented at the NCI in July 1993, Dr Freidman said that if a patient of mine who had been diagnosed with inoperable pancreatic cancer lived 3 months beyond the reported mean of 6 months, he wouldn’t be impressed, whereas survival 6 months in excess of the standard averages would be meaningful. Of course, absolute values for “significance” will vary from cancer to cancer: 6 months of extra life might be unusual for a patient

with a pancreatic neoplasm, but not so for a woman with metastatic breast cancer. In this case, 2 years beyond the mean would, to me, indicate a compelling response to treatment.

Traditionally, the NCI, which sets the standards for oncology worldwide, has not considered survival as a valid endpoint, only objective response as documented by radiographic or other tests. When I presented to the NCI in 1993, for epithelial cancers, the NCI experts defined “response to treatment” as a 50% or greater reduction in tumor size that lasted at least 4 weeks. Unfortunately, as it has turned out, many chemotherapy drugs easily shrink tumors to this degree and within this time span, but the patients live no longer than if they had received no therapy. Tumor reduction, in chemotherapy studies, generally does not translate into longer life for the patient. Though the phenomenon has long perplexed the research establishment—logically, one expects if tumors shrink, patients should live longer—scientists now recognize that chemotherapy may kill the less aggressive population of cells and shrink tumors nicely, but then leave a small, drug-resistant clone that quickly takes over and proliferates explosively. So the selection for more virulent cells cancels out the initial benefit. In any event, I have long believed the definition of response of a 50% reduction lasting 4 weeks to be rather meaningless, as patients care more about their length of life, not necessarily the size of their tumors.

Dr Isaacs and I learned early on that with our treatment, at times, tumors will reduce significantly or blood parameters will improve, but at other times, the disease does not objectively regress but instead stabilizes. We find that patients in the “stabilized” group often survive as long as those enjoying radiographic or laboratory evidence of benefit, as long as they adhere to their nutritional regimen.

During my 1993 NCI presentation, though I discussed a number of patients from my practice with documented disease reduction on standard testing, I also described several cases with long-term stabilization without proof of regression. I argued that in such instances, the unusual survival should be considered as a response, regardless of what the radiographic or blood tests showed. Today the scientists at the NCI have reworked their definition of response to include not only radiographic or laboratory evidence of regression, but significantly enhanced survival with or without correlating “objective” documentation.

Over the years, I have repeatedly heard the claim that Dr Isaacs and I must be processing and treating thousands and thousands of new cancer patients each year to obtain the results illustrated by these case reports. In fact, a good friend of mine recently remarked that I must be seeing “350-450” new cases of pancreatic cancer yearly, because we are well known for our success with this particular illness. This is simply not the case. In reality, we see no more than 3-5 new cases a year.

Following is just a sampling of several case reports that have been culled from our files.

BREAST CANCER

According to *Harrison's Principles of Internal Medicine*,

216,000 women developed breast cancer in the United States in 2004, and 40,000 died, making the disease the most common malignancy (other than skin) among women.^{9(p516)} Though surgery can cure approximately 50% of those diagnosed initially with localized disease, for patients with evidence of distant spread, breast cancer remains ultimately incurable despite advances in chemotherapy, hormonal intervention, and blockade and targeted therapies such as Herceptin. The 5-year survival for women with evidence of metastatic disease at the time of diagnosis is around 14%, and in the conventional medical world, even the group of survivors eventually will die of their cancer. In the DeVita textbook, *Cancer: Principles and Practice of Oncology*, the authors report an average lifespan for women diagnosed with metastatic breast cancer of 2-3 years, with some variability.^{10(p1700-1701)} Poor prognostic indicators include an incomplete or short-lived response to prior therapy, negative hormone receptor status, involvement of a major organ like the liver or brain, and multiple sites of involvement.

Patient #1: A 16-year Survivor

Patient #1 is a 64-year-old woman with a strong family history of breast cancer. She had been in good health when in the fall of 1986, routine mammography revealed a suspicious mass in the left breast, confirmed by biopsy as ductal carcinoma in situ. Although her surgeon suggested a modified radical mastectomy, the patient insisted a lumpectomy be done. The surgeon agreed, and removed the cancerous tumor. Since she had no evidence of metastatic disease, her doctors did not recommend additional adjuvant treatment.

She subsequently did well until July of 1989, when her physician detected a mass in the right breast. She underwent lumpectomy with excision of a 3-cm right axillary mass that proved to be a poorly differentiated adenocarcinoma, estrogen and progesterone receptor-negative, invading and largely replacing the adjacent lymph node. After surgery, an abdominal ultrasound revealed a density on the right lobe of the liver consistent with metastatic disease. A needle biopsy of the hepatic lesion confirmed metastatic carcinoma, and a bone scan showed “multiple focal areas of increased activity in the spine consistent with metastatic carcinoma.”

Patient #1 then began chemotherapy with cyclophosphamide, adriamycin, and 5-fluorouracil (CAF), a very aggressive protocol, which she tolerated poorly. In late 1989, after completing 3 cycles, she refused further treatment and for several months, she did nothing before visiting Stanford in the spring of 1990 for a second opinion. There, after reviewing the previous biopsies and scans, the physicians concurred with the diagnosis of metastatic disease to the liver. The Stanford note reports, “The diagnosis is confirmed and the liver involvement has been documented by the Stanford Pathology Laboratory.”

Her doctor at Stanford recommended she immediately resume chemotherapy with CAF, but once again, Patient #1 refused to consider further orthodox therapy. Instead, after learning of my work, she decided to pursue my program and was first seen in my office in April of 1990.

She was quite ill at the time, suffering chronic pain in her

liver. After returning home and beginning her regimen, the liver pain was so severe she required morphine sulfate (MS Contin, Purdue Pharma) for comfort. She also suffered fatigue and malaise lasting many months, before she finally began to improve. When I saw her for a return evaluation in May 1991—a year after she had begun her nutritional protocol—she felt much stronger, and her abdominal pains had largely resolved. Unfortunately, she began to feel so well that without my knowledge, she subsequently discontinued her protocol, assuming she was “cured.” In early July 1991, she called me very distraught, having just suffered a grand mal seizure, and admitted she had been off her protocol for several months. A CT scan of the brain revealed a high-density epidural mass in the left sphenoidal ridge and a small, low-density area in the right temporoparietal region. The radiology report reads, “Both areas were heterogeneously enhanced with contrast medium and appear to be metastatic brain lesions.”

Her doctors immediately recommended radiation to the brain, which Patient #1 refused. Instead, she resumed her full nutritional program with renewed dedication, quickly improved, and never had another seizure. Follow-up CT scans of both the head and abdomen in April 1992, less than a year after her recurrence, were completely normal—the previously noted liver and brain tumors were gone. The report of the head CT reads, “There is no mass or mass effect. . . . There is no evidence of metastatic disease. . . . Normal CT scan of the head.” The summary of the abdominal scan states, “Normal CT scan of the abdomen.”

Since that time, Patient #1 has had an up-and-down history on my program, with periods of good compliance and periods of less than good compliance. I haven’t seen her in my office in some years, but I’ve heard from friends that she is still doing well and still taking enzymes. Our last formal contact with her was in October of 2005, when she appeared to be doing fine, 15 years after her diagnosis of terminal metastatic breast cancer.

Her course with such terrible disease is certainly unusual. Patient #1 also served as her own “control”; when she followed the program she did well, and when she didn’t comply, the cancer came back with a vengeance. The disease then completely regressed when adherence to therapy improved.

We usually tell new patients who come to us with a history of metastatic cancer that they need to follow their nutritional regimens indefinitely, and must never assume they are completely free and clear. Dr Isaacs and I think of cancer as a chronic degenerative disease, akin to diabetes, that can be managed successfully for years as long as patients follow their diet and take their enzymes. When a patient fails to do that, as in this case, cancer can return and cause havoc. Renewed dedication to the treatment can usually get the situation back under control.

Especially given her compliance lapses, Patient #1’s survival is extraordinary. As the medical literature documents, breast cancer, when metastatic to either the brain or liver, is a deadly disease. In a series of patients with brain metastases specifically, Lentzsch et al report a median survival of 23 weeks for those with more than 1 lesion, despite aggressive conventional treatment.¹¹ In a group of patients with at least 1 lesion receiving supportive care only, the

authors describe a median survival of 5 weeks.

Eichbaum et al studied a group of 350 women with breast cancer that had metastasized to the liver.¹² The authors describe a median survival, regardless of the conventional treatment given, of 14 months, somewhat better than the numbers for brain metastases, but still dismal.

In this case, Patient #1 had evidence of liver, brain, and bone metastases, as deadly a combination as can be imagined.

UTERINE (ENDOMETRIAL) CANCER

In 2004, 40,300 new cases of cancer of the uterine lining were reported, along with 7,000 deaths.^{9(p556)} Fortunately, in about 75% of all cases, the disease is diagnosed at an early stage when surgery can be curative. For decades, radiation to the pelvis has been routinely recommended as adjunctive postsurgical treatment for localized endometrial cancer. However, the data from the only 2 controlled clinical trials completed to address the effect of radiation, published in 1980¹³ and 2000,¹⁴ respectively, show overall no survival advantage compared to surgery alone. In certain subgroups, the authors report patients receiving radiation actually have shortened survival times.

Once metastatic, uterine cancer resists chemotherapy and usually kills quickly, with a median survival reported in the range of 6-8 months, and a 5-year survival rate at 5% or less. Hormonal blockade with the synthetic progesterone megestrol acetate (Megace, Bristol-Myers Squibb) or a similar drug can offer temporary benefit in some 20% of patients with widespread disease, but the responses are usually short-lived.

Patient #2: A 16-year Survivor

Patient #2 is a 62-year-old woman who had been in good health when in the fall of 1990, she required hospitalization for 2 episodes of deep venous thrombosis. She was placed on warfarin sodium (Coumadin, Bristol-Myers Squibb), but shortly thereafter suffered an episode of severe vaginal hemorrhage. When the bleeding persisted, in December 1990, she underwent a dilation and curettage (D&C), which revealed endometrial carcinoma. After a CT scan in January 1991 showed extensive abdominal and pelvic lymphadenopathy, she underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy.

The pathology report describes endometrial adenocarcinoma with areas of squamous differentiation, high nuclear grade (International Federation of Gynecology and Obstetrics [FIGO] grade III), and papillary serous carcinoma, one of the most lethal uterine malignancies. The tumor had spread to the left ovary, obliterating the fimbriated end of the left fallopian tube. Biopsies of the peritoneal cul de sac as well as the rectal serosa confirmed metastatic disease, and due to the extent of metastasis, her doctors warned of a very poor prognosis.

Postoperatively, Patient #2 met with a radiation oncologist who insisted treatment begin at once. Before agreeing to any therapy, Patient #2 decided to consult with a second oncologist in a Southern tertiary care center. Once again, radiation was aggressively pushed as essential to delay spread of her aggressive disease.

However, Patient #2 decided to refuse all orthodox treatments, instead choosing to medicate herself with a variety of nutritional supplements, including high-dose vitamin C and red clover tea.

An abdominal MRI in March 1991 showed a “decrease in degree of periaortic lymphadenopathy with persistent evidence of matted lymph nodes.” Pelvic MRI documented “decrease in the degree of diffuse pelvic lymphadenopathy although there is persistent evidence of pelvic mass lesion most notable in the left hemipelvis. There is evidence of surgical defect presumably from previous hysterectomy.” So with surgery, there had been improvement, though extensive disease clearly remained.

About that time, after learning of our work, Patient #2 decided to pursue my therapy. When first evaluated in my office in April 1991, she reported persistent fatigue, a recent weight loss of 15 lbs, “terrible night sweats,” and poor sleep.

Patient #2 subsequently followed her regimen with great determination. Seven months later, in December 1991, repeat MRIs showed no change in the periaortic lymphadenopathy as compared with the study of March 1991, but significant regression of the pelvic adenopathy and the pelvic mass in the left hemipelvis. The official report states, “Compared to the study of [March 1991], there is continued improvement with near complete resolution of previously seen pelvic lymphadenopathy. Currently, there is no appreciable residual mass lesion present within the left hemipelvis.”

Thereafter, Patient #2 continued her nutritional program diligently, with reported improvement in her general health. MRI studies of the abdomen and pelvis in January 1993, after she had completed 20 months on therapy, indicated that the previously noted extensive disease had completely resolved. The pelvic scan revealed, “There is no identified pelvic lymphadenopathy.” The official report of the abdominal MRI states, “There is no evidence of significant periaortic or periportal lymphadenopathy.”

MRI studies completed 14 months later, in March 1994, confirmed “no distinct evidence of metastatic or recurrent disease.”

Patient #2 followed her regimen faithfully until early 1997, when I last had formal contact with her. At that time, 6 years from her diagnosis of metastatic aggressive histology endometrial cancer, she remained disease-free and generally in good health. She subsequently continued her therapy in a reduced way, and at last report, now nearly 16 years from diagnosis, is alive and apparently doing well.

This case is straightforward: the patient was diagnosed with extensive, aggressive histology uterine cancer, including papillary serous, one of the most deadly subtypes. The surgeon could not excise all the visible cancer, as MRI studies after surgery documented. She then experienced complete regression of her advanced disease while following her nutritional program and remains alive 16 years later.

NON-HODGKIN'S LYMPHOMA

Traditionally, researchers have differentiated Hodgkin's disease from the non-Hodgkin's lymphomas, though both are malignancies of the lymphocyte cells of the immune system. For

2006, the American Cancer Society predicted 58,870 new cases of non-Hodgkin's lymphoma, and 18,840 deaths.¹⁵ This umbrella term actually includes well over a dozen different types that range from the very indolent to very aggressive, potentially deadly disease.

Patient #3: A 15-year Survivor

Patient #3 is a 64-year-old woman from the Southwest who in the fall of 1987 first developed vague abdominal discomfort. When the pain persisted, in January 1988, her physician referred her for a CT scan, which revealed several large abdominal tumors. In January 1988, she underwent exploratory surgery, hysterectomy, and bilateral salpingo-oophorectomy, with resection of 2 large masses attached at the mesentery together measuring 9 cm x 8 cm x 8 cm in diameter. The pathology report describes the lesions as consistent with diffuse mixed lymphoma, mixed small and large cleaved cell type, a very aggressive form of the disease.

Patient #3 then completed 6 months of chemotherapy with methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin (MACOP-B), an intensive regimen consisting of 5 different chemotherapy drugs and the steroid prednisone. Repeat CT scans in August 1988, at the completion of treatment, were negative and her doctors assumed her to be in remission. Subsequent scans were clear until May of 1991, when a CT scan picked up 2 nodules in the lungs, the largest in the lingual, measuring 1.6 cm, the smaller in the left lower lobe, measuring 0.6 cm. In addition, the report describes “small periaortic lymphadenopathy at the level of the kidneys,” which had been noted on prior scans. A chest CT in July 1991 revealed a 2.5 cm x 2 cm mass in the left hilar area, an abnormality of the lingula, and a left lower lobe mass: “(1) Left hilar mass and posterior left lower lobe nodule. (2) Progressing mass and associated atelectasis or infiltrate in the lingula.”

Although her doctors discussed resuming chemotherapy, Patient #3 had “had enough.” After learning of our work, she decided to pursue our program.

When I saw Patient #3 in my office in September 1991, she generally felt well and thereafter proved to be a very compliant patient. Six months after beginning her regimen, in March 1992, a repeat CT scan of the chest demonstrated a small pleural-based density associated with the anterior left cardiac margin, approximately 1 cm x 1.5 cm in size, that had significantly regressed since the scans of 1991. And the additional lesions that had previously been described were not evident. An abdominal CT scan revealed “slightly prominent nodes on the para-aortic area measuring up to 1 cm in diameter” but no other worrisome lesions.

In September 1992, after she had been on her program a full year, CT studies of the abdomen and pelvis were clear, but the chest CT showed a “3.5 cm x 2 cm density in the left mid lung and lower lung field which, according to the previous dictation, has increased in size significantly and, therefore, must be considered an active lesion.”

When I discussed the findings with Patient #3, she seemed determined to continue with her nutritional program only,

expressing no interest in pursuing any other treatment. After I made some adjustments to her protocol, she decided to forgo future CT scan studies. She said they created enormous anxiety, and she had no intention of changing treatment, whatever the tests showed.

Over the next decade, Patient #3 continued her regimen, with excellent compliance. She generally enjoyed good health, despite some ongoing problems I attribute to her earlier chemotherapy, such as a persistent irregular heart rhythm and episodic respiratory symptoms, including shortness of breath with exertion. One of the drugs in the MACOP-B regimen, daunorubicin, has been associated with heart damage in a significant number of patients, and bleomycin often provokes pulmonary fibrosis, sometimes years after treatment. In January 2004, she underwent cardiac and pulmonary evaluations, which revealed no significant underlying disease. A chest x-ray at that time—her first radiographic study since the CT scan of 1992—showed a “small left apical pneumothorax. Chest x-ray is otherwise radiographically normal.” The previously described masses seen on CT were gone, and I attribute the area of collapse to bleomycin use years earlier.

Patient #3, now on her nutritional regimen for more than 15 years, continues to be in good health with apparent total resolution of her once aggressive disease. She enjoys her life, is grateful that she has lived to see her children grow, marry, and raise their own children.

The diffuse and diffuse mixed types represent particularly aggressive forms of lymphoma that frequently come back after even the most aggressive of chemotherapy regimens. *Harrison's* reports that the disease recurs in nearly 50% of treated patients with this diagnosis, and of these, fewer than 10% will respond to additional chemotherapy.^{9(p650-651)} Certainly this patient faced a grim future when the CT scan studies in 1991 confirmed new disease.

RENAL (KIDNEY) CANCER

In the United States, 36,000 new cases of kidney cancer and 12,500 deaths were reported in 2004.^{9(p641)} Cigarette smoking predisposes to the disease, with up to 20% to 30% of cases being linked to the habit. Researchers have suggested associations with obesity, polycystic kidney disease, von Hippel Lindau Disease, and certain genetic aberrations. In recent years, though the incidence has been increasing steadily, no clear-cut environmental risk other than cigarette smoking has been confirmed.

Renal cell carcinoma, the most common form of kidney cancer, accounts for 90% to 95% of all cases. In this type, the disease begins in the epithelial lining cells of the proximal tubules and, if localized, can be cured in well over 50% of patients with surgery alone.^{10(p1364)} Once the disease metastasizes, it usually spreads quickly, with deadly results. Conventional therapies such as chemotherapy and immune modulation offer little benefit. As *Harrison's* reports,^{9(p642)} “Investigational therapy is first-line treatment for metastatic disease as no immune approach or chemotherapeutic agent has shown significant antitumor activity.” Interleukin-II, heralded as a miracle cure in the mid 1980s

based on anecdotal evidence, in controlled clinical trials worked no better than placebo.

Patient #4: A 15-year Survivor of Renal Cell Carcinoma

Patient #4 is an 82-year-old man who had a history pertinent for celiac disease, gout, and chronic borderline anemia. In October of 1990, his primary physician noted an abdominal mass during a routine yearly physical examination. Subsequent MRI and CT scan studies revealed a 14-cm tumor in the left kidney, with no evidence of metastases. Chest x-ray and bone scan were both clear, and in late October 1990, Patient #4 underwent exploratory laparotomy and left nephrectomy. Pathology studies confirmed renal cell carcinoma, with 1/1 adjacent nodes positive for invasive cancer.

Patient #4 was then referred to a major New York medical center for additional evaluation and treatment. There, in December 1990, he agreed to enter a clinical trial testing alpha-interferon, an immune stimulant, against kidney cancer. After repeat chest and abdominal CT scans showed no evidence of residual or recurrent disease, Patient #4 began an 8-cycle course of intensive interferon, which he completed in August of 1991.

Thereafter, Patient #4 did well until November 1991, when he noticed a lump in the left parietal-occipital region of the skull that rapidly enlarged over a period of several days. In early December, needle aspiration of the mass confirmed “adenocarcinoma, consistent with metastatic renal tubular carcinoma.”

A subsequent CT of the head indicated that the tumor had penetrated through the skull into the cranium, as the report states: “There is a lytic lesion within the left parietal bone with an associated enhancing soft tissue mass, consistent with a metastasis. There is intracranial extension of the enhancing soft tissue, as well as extension into the subcutaneous tissues of the left parietal scalp.”

A bone scan revealed “a large focal area of increased radiopharmaceutical uptake with a photopenic center consistent with metastatic disease in the left occipital region of the skull.” A CT scan of the chest indicated “Small nodule at the left lung base . . . which may be an area of fibrosis as described. Two other smaller densities in the middle lobe and the left lower lobe as described of questionable significance.” However, these lung findings had not been reported on the chest CT of December 1990.

Patient #4 then began a 1-month course of radiation to the skull mass, totaling 4,000 rads and completed in January 1992. Despite the treatment, the tumor regressed only marginally. Patient #4, having been told he had incurable disease, decided to pursue my protocol. When we first met in January 1992, only a week after he had finished radiation, Patient #4 reported significantly diminished energy, along with a 20-lb weight loss during the previous 6 weeks. On exam, I immediately noticed a lemon-sized mass sticking out of his skull in the left parietal area.

Shortly thereafter, Patient #4 began his nutritional protocol, complied well, and within weeks reported a significant improvement in his energy and well being, as well as a 20-lb weight gain. After he was on his nutritional protocol for 3 months, the large skull mass completely resolved. A repeat bone scan in June 1993,

after Patient #4 had completed 16 months of treatment, revealed “no evidence of bony metastatic disease.” Not only had the lesion disappeared, but the underlying skull had healed. Today, nearly 15 years since he first consulted me, Patient #4 remains completely adherent to his treatment and is in excellent health and cancer-free.

Several points bear mentioning. Renal cell carcinoma, once metastatic, is a very deadly disease: DeVita et al report a median survival of only 50 days for patients with stage IV kidney cancer, despite treatment.^{10(p1369)} This neoplasm resists not only chemotherapy and immunotherapy, but radiation as well. In this case, Patient #4’s doctors suggested radiation not as a potential cure but as palliation, hoping to slow the spread of the tumor into the brain. In any event, the response was negligible. While some radiation oncologists report that at times, the benefit of radiation therapy might continue for up to 2 months, Patient #4 showed significant response only after his third month on his nutritional program. Furthermore, although his radiologists initially downplayed the new findings on the chest CT in late 1991, in retrospect these lesions may have indicated the beginnings of explosive spread.

OVARIAN CANCER

In 2004, 25,580 women in the United States developed ovarian cancer, and 6,000 died from the disease, making it the leading cause of gynecological cancer deaths in women.^{9(p553)} Ovarian cancer tends to occur in family clusters, with some 5% of all cases linked to inherited genetic aberrations, particularly mutations in the BRCA1 and BRCA 2 genes—mutations long associated with breast cancer as well. The protein products of 2 these alleles normally serve as tumor suppressors, so irregularities in the DNA encourage carcinogenic transformation.

The disease has also been linked to infertility, use of fertility-enhancing drugs such as Clomid, and nulliparity. Each pregnancy reduces the risk, as does breast feeding. Regular use of oral contraceptives actually reduces the risk of ovarian malignancy, while hormone replacement therapy doesn’t influence incidence either way, despite earlier concerns.

Ninety percent of women diagnosed with strictly localized disease survive 5 years, many of them cured by surgery alone. Once the disease spreads, ovarian cancer can be very aggressive, with fewer than 5% of stage IV patients living 5 years despite aggressive treatment.^{10(p1604)} Chemotherapy regimens that include one of the taxane derivatives, given along with platinum agents such as carboplatin, cut the recurrence rate for localized tumors and marginally improve survival for patients with advanced disease.

Patient #5: A 10-year Survivor

Before developing cancer, Patient #5 had a long history of neuro-muscular symptoms dating to 1979, when she first developed a mass in her left calf that was associated with muscle pain, atrophy, and numbness. As the symptoms worsened, she consulted numerous physicians at numerous centers. Though multiple

muscle biopsies had all been unrevealing, she was nonetheless treated empirically and unsuccessfully with a variety of drugs, including prednisone. In 1985, she sought another evaluation at the Mayo Clinic, where another muscle biopsy confirmed polymyositis. After she was diagnosed with motor and sensory neuropathy, type II, Patient #5 began another course of prednisone but with little improvement, followed by 6 months on Imuran. The latter drug did nothing for her disease, but did lead to weight gain, insomnia, and anxiety.

As her symptoms worsened, Patient #5 decided to seek treatment with me for her neuromuscular problems. When she first came to my office in 1989, she had been off all medications for 3 years, during which time her symptoms of weakness, nerve pain, and numbness continued to progress. When I first saw her, she had no gynecological problems other than the history of a hysterectomy for uterine fibroids.

I designed a protocol to treat this patient’s muscle and neurological problems without the high doses of enzymes we use against cancer. Subsequently, Patient #5 complied well with her program, and when I saw her for a return visit in August 1989, she reported that her condition, which had worsened without respite over the previous 10 years, had improved significantly. She described a “20%” overall gain in motor strength and calf thickness, a marker her previous doctors had used to track her decline. The proximal muscle weakness in both legs had reversed to the point that she could stand from a sitting position for the first time in years. However, on exam I detected a small pelvic mass and told her she needed to follow up with a gynecological evaluation upon returning home.

Some weeks later, in early fall, an ultrasound revealed a 7 cm x 8 cm cystic lesion posterior to the bladder. In early November 1989, at the Moffitt Cancer Center in Tampa, Fla, she underwent exploratory laparotomy and was found to have extensive malignant disease throughout her pelvis and abdomen. Her surgeon proceeded with bilateral oophorectomy, omentectomy, and extensive lymphadenectomy of pelvic, periaortic and precaval lymph nodes. The pathology report describes “Omentum diffusely infiltrated by papillary serous carcinoma” of ovarian origin, as well as tumor in both ovaries that involved both fallopian tubes. Cancer had infiltrated into all 21 of 21 nodes evaluated, and peritoneal washings were positive for “metastatic adenocarcinoma consistent with ovarian primary.”

After surgery, Patient #5 met with an oncologist who strongly recommended intensive chemotherapy, but she decided to refuse all conventional treatment, instead choosing to begin the cancer version of my therapy. At that point, I redesigned her regimen to include high doses of pancreatic enzymes throughout the day.

In December 1989, her oncologist wrote a summary note to me, which accompanied the records of her recent hospitalization. In his letter, he said, “She is diagnosed as having a Stage IIIC Grade I papillary serous cystadenocarcinoma of the ovary. I have recommended that she receive chemotherapy. She would be a candidate for GOG [Gynecologic Oncology Group] Protocol 104 intravenous

cisplatin and cyclophosphamide versus intraperitoneal cisplatin and cyclophosphamide. Mrs _____ unfortunately did not wish to pursue the idea of chemotherapy.”

She thereafter followed her program diligently for 6 years. By the mid 1990s, her muscle weakness began to progress once again, making return trips to New York difficult, though she continued on the regimen and we worked together by phone. We last spoke in August of 1999, when she wrote after hearing me on the radio. She was 78 at the time, able to walk with a leg brace, and otherwise doing fine, apparently cancer-free nearly 10 years after her diagnosis of extensive ovarian malignancy.

Regarding ovarian cancer patients such as this, DeVita et al report, “Patients with stage III disease have a 5-year survival rate of approximately 15%-20% that is dependent in large part on the volume of disease present in the upper abdomen.”^{10(p1604)}

In this patient’s case, the disease did extend into the upper abdomen at the time of diagnosis. Furthermore, these survival statistics refer to patients treated with aggressive chemotherapy, which Patient #5 refused, choosing to follow only my regimen. Her prolonged disease-free survival can be attributed only to her nutritional program.

PANCREATIC CANCER

According to *Harrison’s*, in 2004, pancreatic cancer killed 31,270 Americans, making it the fourth major cancer killer.^{9(p537)} It is particularly virulent, killing 98% of all patients within a year of diagnosis. The cause still eludes orthodox thinkers, though over the years they have uncovered some clues. Cigarette smoking increases the risk 3 times, with up to 30% of cases linked to the habit. Chronic pancreatitis and obesity predispose to the illness, as does diabetes mellitus. Experts argue for a genetic component in some families, with approximately 3% to 9% of all cases thought due to such an inherited predisposition.^{10(p1127)}

Ninety percent of all cases begin in the enzyme-producing (exocrine) cells of the pancreas, only 5% to 10% in the endocrine, hormone-secreting tissue. For the most common form, adenocarcinoma of the exocrine pancreas, the conventional medical literature reports an average survival for those with metastatic disease in the range of 3-6 months from the time of diagnosis, while earlier stage patients live 10-14 months on average. The prospects for long-term survival remain dismal whatever the stage.

In the orthodox oncology world, surgical resection of localized adenocarcinoma provides the only prospect for long-term survival, but at the time of diagnosis, most patients already have evidence of widespread cancer and for them, surgery offers no benefit. Chemotherapy does little; the FDA approved Gemzar (Eli Lilly and Co), specifically for the treatment of pancreatic adenocarcinoma after data from clinical trials showed that patients treated with the drug lived an average of 5.6 months, 4 weeks longer than those receiving other forms of chemotherapy.⁷ Researchers did claim that in addition to this slight survival advantage, 29% of Gemzar-treated patients enjoyed an improved “quality of life,” defined as less pain, increased appetite, and an overall slight enhancement of their general “well being.” Though short-lived,

such benefits still represented an advance over previous options for the disease. Recently, investigators at a number of academic centers have reported little additional improvement when they added other powerful chemotherapy agents into the Gemzar mix.

Scientists divide the rarer islet cell tumors into many subtypes, depending on the specific hormone released; for example, insulinomas secrete insulin, glucagonomas, glucagon, and gastrinomas, gastrin. These cancers may secrete these hormone products in dangerous amounts—frequently patients with insulinomas first seek medical advice after repeatedly fainting between meals, when excessive insulin drives so much glucose out of the bloodstream that blood sugar drops precipitously. Whatever the particular type, islet cell carcinomas tend to be less aggressive than adenocarcinomas: even patients with metastatic disease at the time of diagnosis can live 5 years due to its inherently slow progression, but it usually does progress, eventually with fatal results.

Patient #6: A 10-year Survivor

In 1985, Patient #6 had undergone surgery for localized colon cancer but subsequently received no adjuvant radiation or chemotherapy for the disease. He thereafter did very well until he developed a large right neck mass about the size of a golf ball in October 1996 while traveling outside the country. Upon returning to the United States in December 1996 he underwent a biopsy, which confirmed “adenocarcinoma.” His doctors assumed the cancer had metastasized from some abdominal organ, though they weren’t initially certain which one. Patient #6 then traveled to Memorial Sloan-Kettering in New York, where he was seen in early January 1997. There, after the biopsy slides were reviewed and adenocarcinoma confirmed, the pathologist reported the neck disease most likely represented metastasis from a new primary tumor, not recurrent colon cancer, as the note describes “metastatic poorly differentiated adenocarcinoma with focal signet ring cell features to lymph node. Possible primary sites include lung, stomach and pancreas.”

Patient #6 then underwent CT scanning of the chest and abdomen as well as bronchoscopy, all of which were unrevealing. A CT scan of the neck demonstrated “Pathologic appearing adenopathy within the right posterior triangle.”

A PET scan a week later revealed “(1) Abnormal FDG Pet scan showing focal FDG uptake in the right posterior neck, consistent with lymph node metastasis. (2) Focal uptake seen in the right upper quadrant, just anterior to the right kidney, may be due to primary tumor. The location could be in the head of the pancreas or the second part of the duodenum.”

At this point, after the Memorial doctors concluded the primary to be most likely pancreatic cancer, they suggested a conservative approach, holding off treatment until the disease further advanced. However, Patient #6 had learned of our treatment approach, decided to proceed with us, and first consulted with me in January 1997. Thereafter, he followed his program diligently, with good results. Follow up MRIs of the abdomen and pelvis at Memorial in July and October 1997 revealed no evidence of cancer anywhere. The October report reads, “Since the previous study of

7/___/97: (10 No significant interval change is appreciated. (2) No evidence for neoplasm in the abdomen. (3) No abnormalities are identified in the pelvis.”

Patient #6 continued his aggressive protocol for 3 years, before winding down to a maintenance regimen. Today, nearly 10 years after he started his nutritional regimen, he appears to be in excellent health, enjoys retirement, and remains free of his once life-threatening cancer.

This case is very straightforward. Biopsy confirmed metastatic carcinoma, considered by the Memorial experts most likely, based on the PET scan, to be of pancreatic origin. The patient followed his regimen faithfully; subsequent scans showed no evidence of disease, and he remains cancer-free to date.

Editor's note: This article contains only a small selection of the 31 case reports Drs Gonzalez and Isaacs submitted to Alternative Therapies. To read all of the case reports, visit our website: www.alternative-therapies.com.

REFERENCES

1. Beard J. The action of trypsin upon the living cells of Jensen's mouse tumor. *Br Med J*. 1906;4:140-141.
2. Campbell JT. Trypsin treatment of a case of malignant disease. *JAMA*. 1907;48:225-226.
3. Cutfield A. Trypsin treatment in malignant disease. *Br Med J*. 1907;5:525.
4. Beard J. *The Enzyme Treatment of Cancer*. London: Chatto and Windus, 1911.
5. Morse FL. Treatment of cancer with pancreatic extract. *Wkly Bull St.Louis Med Soc*. 1934;28:599-603.
6. Gonzalez NJ, Isaacs LL. Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. *Nutr Cancer*. 1999;33:117-124.
7. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15:2403-2413.
8. Saruc M, Standop S, Standop J, et al. Pancreatic enzyme extract improves survival in murine pancreatic cancer. *Pancreas*. 2004;28:401-412.
9. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo, DL, Jameson JL. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005:516.
10. DeVita VT, Hellman S, Rosenberg SA. *Cancer: Principles and Practice of Oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:1700-1701.
11. Lentzsch S, Reichardt P, Weber F, Budach V, Dorken B. Brain metastases in breast cancer: prognostic factors and management. *Eur J Cancer*. 1999;35:580-585.
12. Eichbaum MH, Kaltwasser M, Bruckner T, de Rossi TM, Schneeweiss A, Sohn C. Prognostic factors for patients with liver metastases from breast cancer. *Breast Cancer Res Treat*. 2006;96:53-62.
13. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma. *Obstet Gynecol*. 1980;56:419-427.
14. Creutzberg CL, van Putten WLJ, Koper PCM, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. *Lancet*. 2000;355:1404-1411.
15. American Cancer Society. What are the key statistics about non-Hodgkin lymphoma? Available at: www.cancer.org. Accessed November 5, 2006.
16. Spillane, AJ, Thomas JM, Fisher C. Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. *Ann Surg Oncol*. 2000;7:218-225.
17. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg*. 2006;244:254-259.