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REPORT TO PHYSICIANS

JANUARY 2005 Vol. 50, No. 1

Oncology

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Treatment for brain metastasis is now faster, safer, and more precise than in the past.



New Perspectives on Brain Metastasis

Today, a diagnosis of brain metastasis signals another round in a person's fight against cancer rather than the end of the battle.

by Rachel Williams

Anyone who walks past the waiting room toward the "Authorized Personnel Only" sign posted over the closed double doors of the operating rooms probably will notice family members and friends waiting for word about

loved ones undergoing surgery for metastatic brain tumors. But no longer is it the anxiety-producing wait that it once was.

Today, brain metastasis—even multiple metastases—is not an automatic death sentence, and its treatment, while still not to be taken lightly, has become safer, minimally invasive, and more effective than it was not many years ago.

"Multiple tumors in the brain do not have as bad a prognosis as one would think," said Jeffrey Weinberg, M.D.,

(Continued on next page)

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New Perspectives on Brain Metastasis

(Continued from page 1)

assistant professor in the Department of Neurosurgery at The University of Texas M. D. Anderson Cancer Center. “A recent study showed that a patient who has two or three lesions that can be removed actually has the same prognosis as someone who has only one brain tumor.”

In the past, the only treatment for multiple metastases was whole brain radiation, which on its own had little effect on survival. While that is still the standard treatment for four or more brain tumors, there are now a variety of effective treatment modalities for people who have fewer than four tumors.

“With a small, finite number of tumors, it may be better to treat the individual brain tumors themselves rather than the whole brain when possible,” Dr. Weinberg stated.

He explained that while whole brain radiation has benefits such as treating micrometastases (individual cells that can eventually grow into brain tumors), today it is most often used in conjunction with other treatment modalities, such as surgery and radiosurgery.

“Surgery and radiosurgery allow treatment to be directed at the tumor itself,” said Dr. Weinberg. “Because of technological advancements, both are now minimally invasive and have lower risks.” At M. D. Anderson, multidisciplinary teams that include radiation oncologists and neurosurgeons design treatment plans tailored to the patient’s individual situation.

Imaging Techniques Improve Precision

Computer-assisted surgery has made brain surgery faster, safer, and more precise. Magnetic resonance imaging allows neurosurgeons to see beneath the skull before the incision is made and locate the tumor exactly. Ultrasound provides real-time imaging of the brain as the surgery is being performed. Because of the precision, surgeons can make smaller bone openings, approach the tumor more precisely, and more completely resect it.



M. D. Anderson neurosurgeons **Dr. Jeffrey Weinberg (l)** and **Dr. Frederick Lang** perform surgery to resect a brain tumor.

Advanced operative and imaging technology also allows doctors to map and speech, motor, and sensory areas of the brain before surgery and thereby preserve or avoid them during surgery. Furthermore, they can perform the surgery on patients who are awake if need be in order to better identify speech control areas of the brain.

“We’ve really perfected brain surgery to be relatively safe, even for many lesions that previously were considered unresectable,” said Frederick Lang, M.D., associate professor in the Department of Neurosurgery.

While surgery now involves fewer risks and is less invasive, radiosurgery avoids the risks of a craniotomy altogether and requires only local anesthesia. This highly localized treatment is a same-day procedure.

At M. D. Anderson, radiosurgery is delivered by a team of neurosurgeons and radiation oncologists. Linear accelerators (Linac) are used in conjunction with stereotaxis that allows doctors to align exactly the correct angle and distance for directing radiation beams. The multiple low-dose beams converge from various angles, delivering to the tumor a very high

dose of radiation. While radiosurgery does not actually remove the tumor, it damages the DNA so badly that the tumor is eradicated.

Weighing the Options

There is an ongoing debate about whether surgery or radiosurgery is the better option for treating brain metastasis and under what circumstances. In actuality, each has its own advantages and disadvantages.

Dr. Lang summarized the pros and cons: “The advantage of removing a tumor surgically is that it is taken out in one swoop and people tend to recover faster from swelling and neurocompromise. The disadvantage is that it requires invasive surgery.

“Radiosurgery is lot easier and avoids many of the problems of invasive surgery, but it does not eliminate the tumor immediately. It sometimes takes three or four months to shrink, causing the patient to deal with the tumor’s symptoms longer and to possibly need steroids for a longer period. The follow-up can be more complicated with radiosurgery than with surgery because of the risk of destroying surrounding tissue.”

Cancer Screening Guidelines

M. D. Anderson Cancer Center recommends the following guidelines for cancer screening:

Breast cancer:

- Begin annual mammograms and clinical breast exams at age 40.
- Clinical breast exam every one to three years from age 20 to 39.
- Try to schedule clinical breast exam at the time of regularly scheduled mammogram.
- For women at increased risk of breast cancer, screening may begin earlier and/or may be required more frequently.

Colorectal cancer:

Beginning at age 50, men and women should follow one of the examination schedules below:

- A colonoscopy every 10 years (preferred by M. D. Anderson).
- A fecal occult blood test (FOBT) every year.
- A flexible sigmoidoscopy (FSIG) every five years.
- Annual FOBT and FSIG every five years. This combination is preferred over either annual FOBT or FSIG every five years, alone.
- A double-contrast barium enema every five years. *People at moderate or high risk for colorectal cancer (e.g., a strong family history) should talk with their doctor about the need for a different testing schedule.*

Prostate cancer:

- Men should be counseled about the risks and benefits of prostate cancer screening.
- Annual digital rectal exam beginning at age 50.
- Annual prostate-specific antigen blood test beginning at age 50.
- Begin screening at age 45 for men at increased risk (African-American men, men with a family history of prostate cancer).
- Screening is not recommended for men with a life expectancy of less than 10 years.

Cervical cancer:

- Annual Pap test with pelvic exam beginning at age 18, or when sexual activity begins.
- Depending on risk factors, after three or more consecutive exams with normal findings, a physician and patient may choose to do them less frequently.
- Some healthy women with normal Pap tests who have had a hysterectomy for benign disease may be screened less frequently than annually.

Endometrial cancer:

- Screening is not recommended for most women.
- For women with hereditary non-polyposis colorectal cancer, annual endometrial biopsy is recommended beginning at age 35.

Ovarian cancer:

- Benefits of screening for women at average risk have not yet been proven, and screening is therefore not recommended.
- For women with a hereditary ovarian cancer syndrome, annual or semi-annual pelvic exam, CA 125 blood test, and transvaginal ultrasound may be considered.

Skin cancer:

- Monthly self-exam beginning at age 18.

Thanks to treatment advances, both surgery and radiosurgery are now minimally invasive and relatively safe.

Radiosurgery is optimal for very small lesions, particularly those located deep in the brain, which are hard to find, much less excise surgically. It can't, however, be used on tumors larger than three centimeters because too large an area of brain tissue surrounding the tumor may be exposed to radiation.

Tumors that are between one and three centimeters can be treated with either approach. It's not yet clear which approach is optimal, but M. D. Anderson is working on finding out.

"One of the most important things we're doing in brain metastasis is a Phase III clinical trial in which people are randomized to receive either radiosurgery or surgery. We're several years away from finishing that trial, at which time we hope to have some good data to guide these decisions."

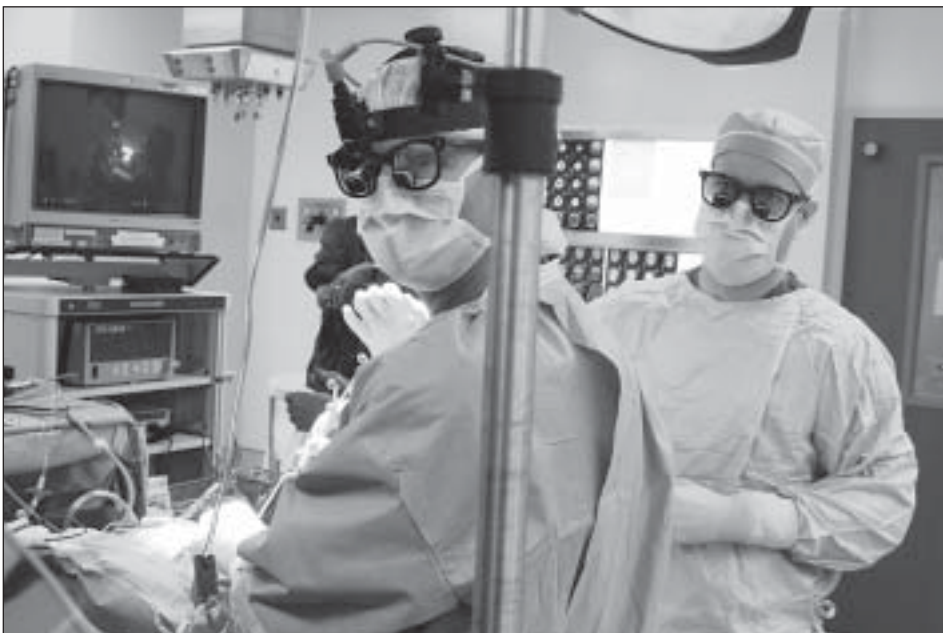
For people with more than one

brain metastasis, M. D. Anderson physicians tend to take a more aggressive approach than many other treatment centers. Most patients with two or three tumors receive a combined surgery/radiosurgery treatment tailored to their particular situation.

"For example, we might take out one large lesion and give radiosurgery to two smaller ones," said Dr. Lang. "Tumors that can be removed are, and those that cannot are treated with radiosurgery. The critical idea is to focally treat all of the tumors, because if you leave one or two behind untreated, the patient is not going to do as well."

Today, brain metastasis can be regarded as another round in a person's fight against cancer, rather than the end of the battle. "There's a completely different perspective about it now," Dr. Lang said. "The chance of living through treatment for brain metastasis today is very high. With these newer, aggressive treatments and better outcomes, the focus can remain on trying to cure the underlying cause of metastatic disease." ●

FOR MORE INFORMATION, contact Dr. Weinberg or Dr. Lang at (713) 792-2400.



Computer-assisted surgery allows surgeons to make smaller bone openings, approach the tumor more precisely, and more completely resect it.

Out of the Darkroom

The field of diagnostic imaging is changing quickly. With advances in molecular imaging and digital technology, today's radiologists are moving out of the darkroom and into the midst of the patient care team.

by Dawn Chalaire

Imagine, if you can, the practice of medicine without imaging studies: no screening tests to alert patients and physicians to the possibility of a serious illness; no computed tomography (CT) scans to help clinicians make an accurate diagnosis; and no follow-up images to ascertain whether a particular treatment is working. With surprising speed, technologies such as CT and magnetic resonance imaging (MRI) have become indispensable, and imaging techniques are continually improving and finding more and more applications in clinical and research situations.

"Over the past five to 10 years, as imaging has gotten better, it has become an integral part of everything we do in clinical cancer care," said Donald A. Podoloff, M.D., professor of nuclear medicine and diagnostic radiology and head of the Division of Diagnostic Imaging at The University of Texas M. D. Anderson Cancer Center.

One indication of the importance of imaging in cancer care is the size of the Division of Diagnostic Imaging at M. D. Anderson. Eight hundred people (107 faculty) in four departments—Radiology, Nuclear Medicine, Diagnostic Imaging Physics, and Experimental Diagnostic Imaging—carry out the division's missions of clinical care, education, research, and prevention. Each day, faculty and staff in the Division of Diagnostic Imaging perform over 480 CT scans and over 100 MRIs.

Measuring Outcomes Molecularly

While the use of CT and MRI continues to increase, the recent emphasis on the development of cancer therapies that target specific molecules or pathways has led to a need for new methods of measuring treatment

outcomes. Whereas CT and MRI reveal anatomic characteristics and physical events, molecular imaging focuses on biological processes such as glucose uptake, metastatic receptor activity, and the expression of genes, proteins, and kinases. This molecular information could be used to evaluate response to treatments such as antiangiogenic agents and apoptotic drugs that do not necessarily result in tumor shrinkage and to verify early on in treatment that molecular therapies are reaching their intended targets.

"I think the power of it clinically will be that, if the hypothesis is correct, after one dose of the drug, you'll be able to tell if the patient will respond before the tumor starts to shrink," Dr. Podoloff said. Such information has "huge economic implications," Dr. Podoloff added, because clinicians will know within days whether an expensive treatment is working, instead of having to wait weeks for the visible results.

Positron emission tomography (PET) is an established method of imaging the regional metabolism of glucose throughout an organ. Because tumor cells are more metabolically active than normal cells, increased glucose uptake can be used to distinguish tumors from normal or necrotic tissue. One of the most promising new technologies to come along in recent years is the combined PET/CT machine. The Division of Diagnostic Imaging currently has two such machines and is in the process of adding two more. These combine the anatomic clarity of CT images with the biologic and metabolic information provided by PET scanning. According



Once ubiquitous, radiology films are quickly being replaced with digital images, said Dr. Donald Podoloff, head of the Division of Diagnostic Imaging.

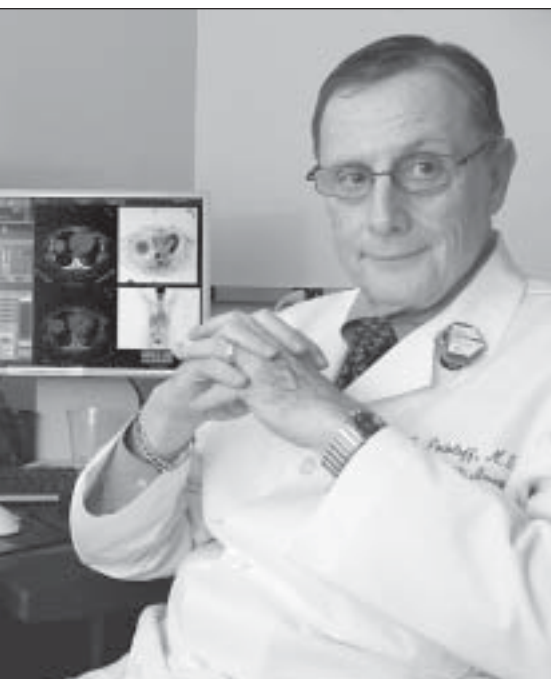
to Dr. Podoloff, PET/CT imaging has had an enormous impact on the way patients with lymphoma and lung, esophageal, and head and neck cancers are monitored. It is also being studied in breast and colorectal cancers and in melanoma.

"PET/CT scanning is a remarkable joining of information that gives you something that is better than either one of them alone," Dr. Podoloff said.

Although anecdotal evidence suggests that PET/CT imaging will change the way certain cancers are managed, studies analyzing the effect of PET/CT imaging on patient outcomes are still ongoing.

Because they combine the technology of PET and CT, PET/CT machines are very expensive. Wai-Hoi (Gary) Wong, Ph.D., a professor in the Department of Experimental Diagnostic Imaging, is developing a PET instrument that could provide resolution similar to that seen with PET/CT, at a fraction of the cost.

Another important advance has been the development of technetium-99m-labeled imaging. David Yang, Ph.D., an associate professor in the Department of Experimental Diagnostic



Molecular imaging could be used to verify early on that molecular therapies are reaching their intended targets.

Imaging has discovered a dimer, ethylene dicysteine, that can be used to link the radioactive compound to a variety of drugs, biologic agents, and other compounds of interest, which can then be seen on x-rays. Although technetium-99m imaging has a lower resolution than PET imaging, it is much less expensive and offers an advantage when studying certain structures in the chest cavity and skull because it does not highlight the heart or brain.

“The appeal of technetium is that it is readily available and relatively cheap. You can use standard imaging; you don’t need a PET scanner for it,” said Dr. Podoloff.

A new metabolic imaging method that measures cellular proliferation and turnover, fluorinated thymidine (FNLT), is currently being evaluated in cancer in a large, multi-institutional Phase III trial.

Investigators in the Department of Experimental Diagnostics are using computational chemistry to develop

biologically active compounds, which will be tested in animals before going on to Phase I studies in humans. To test the activity of these compounds, the researchers are using metabolic imaging methods that reveal receptors on cells, gene expression, and other intracellular targets.

For instance, investigators are developing a PET imaging technique using epidermal growth factor receptor (EGFR) kinase-specific radioactive tracers to measure the activity of novel EGFR-targeted agents. “This will allow us to do regular, noninvasive monitoring of a drug’s activity in a tumor, and may eventually provide a noninvasive selection criteria for study participants as well,” said Juri Gelovani, M.D., chairman of the Department of Experimental Imaging. “The ability to repeatedly monitor EGFR activity at the kinase level should provide a direct measure of drug efficacy in tumor cells as well as measure phospho-EGFR levels in surrogate tissues such as hair and skin.”

M. D. Anderson researchers are also developing imaging techniques for a number of other tissue biomarkers of therapeutic efficacy, such as p53, AKT, Bcl2, and others, as well as for monitoring tumor proliferative activity, apoptosis, gene therapy, stem cell therapies, and adoptive cell immunotherapies.

“Several of these projects are nearly ready for clinical trials,” said Dr. Gelovani.

“Pathologists, with their microarrays, are already doing molecular imaging in vitro,” said Dr. Podoloff. “We want to do the same kind of imaging in vivo. That is what the molecular imaging program is all about.”

Going digital

“In the not-too-distant future,” Dr. Podoloff said recently, “I can envision a time when patients will come in with a small medical chip that has their history, physical, lab data, and x-rays.”

Already, once ubiquitous radiology films are being replaced with digital images saved on computer disks, and clinicians at M. D. Anderson can access imaging studies from anywhere through the institution’s electronic medical records system. This trend toward “radiology without walls,” as Dr. Podoloff calls it, has some interesting implications.

First of all, there is currently no global or national standard program or digital format for imaging studies saved electronically. Patients arrive with information on a disk that may or may not be compatible with the institution’s computers. To address this problem, researchers in the Division of Diagnostic Imaging have developed a universal reader that accepts information in any digital format and converts it into one that can be read by the institution’s radiology software. Dr. Podoloff is also leading an effort to determine whether doing away with radiology films altogether might have an effect on other areas of the institution, particularly in the operating room and in conducting clinical trials.

New role for radiologists

Because of advances in molecular imaging and digital technology, radiologists have moved out of the darkroom and into the midst of the multidisciplinary patient care teams. The practice of radiology is moving away from a modality-oriented approach, in which radiologists are experts in CT or MRI or ultrasound, and toward a disease-oriented approach in which radiologists use all available imaging methods in the imaging of diseases within certain defined anatomic areas.

“My vision for radiology is that it will become more and more disease-oriented and much more molecular,” Dr. Podoloff said. ●

FOR MORE INFORMATION, contact Dr. Podoloff at (713) 745-5153 or Dr. Gelovani at (713) 563-3343.

Equity and Health

M. D. Anderson's Center for Research on Minority Health is asking hard questions about the reasons for inequities in health outcomes and other health disparities – and working toward solutions.

by **Caren E. Blinka**
and **Angelina Esparza**

Cancer, like many diseases, affects anyone regardless of race, creed, color, income, education, or profession.

Although the disease is considered a great equalizer, cancer diagnosis and treatment are not equally available to everyone. “Health disparities” — the recognition that some parts of our population fare worse than others — is a growing concern. Numerous government reports, including “The Unequal Burden of Cancer” and “The Unequal Treatment Report,” both from The Institute of Medicine, document that inequality in health care is a national problem. Many questions, such as what factors affect the incidence and mortality rates of cancer among minorities and the medically underserved, remain unanswered.

Lovell A. Jones, Ph.D., and his colleagues at M. D. Anderson's Center for Research on Minority Health (CRMH) want to answer those questions. As director of the CRMH and a professor in the Departments of Gynecologic Oncology and Biochemistry and Molecular Biology, Dr. Jones feels that the solution to health disparities will require a more holistic approach, one that takes into account cultural beliefs and practices, use of services, socioeconomic, language, and social injustice. “The tendency is to assume that health disparities are due solely to lack of healthcare access, but the answers are much more complicated. Health disparities arise from the interaction of multiple influences,” Dr. Jones said.

The hallmark approach of the CRMH is to incorporate the community as a partner in research development — science that benefits the community. Judging from recent U.S. census data and other demographics, the diversity



“The tendency is to assume that health disparities are due solely to lack of healthcare access, but the answers are much more complicated.”

– Lovell Jones, Ph.D.

of Houston's populations serves as a model for what the nation will look like in 20 years. To address healthcare holistically, providers and researchers need to communicate effectively with people and understand their various cultures and beliefs. The CRMH

African American Nutrition for Life (A Nu-Life) study is an example: its goal is not only to answer the question of why breast cancer has a higher incidence in young African American women, but also to provide the community with tools to implement behavioral changes after the study is completed.

“Another example is a project we're doing with Houston's West African community. As with our other studies, we asked the community about its needs before designing a research agenda. Community leaders expressed the need for a speakers' bureau that would provide cancer information to community members. So we set up a speakers' bureau,” Dr. Jones said. “Over time, we've transitioned from using CRMH speakers to using speakers from within that particular community. Even if we do not launch a study in the West African community for several years, we have provided them with something that is sustainable; there is an infrastructure in place that provides us with long-term opportunities to conduct research with direct community involvement.”

In addition to seeking real-time solutions to community needs, the CRMH also considers future indicators of disease, such as long-term exposure to environmental toxins. The CRMH recently received a \$4.2 million grant from the National Institutes of Health to investigate the role of gene-environment interaction in migrant farm workers and their families. “Most epidemiological studies have focused on the health impact of isolated chemicals; however, understanding the interplay between individual chemicals, the environment, and an individual's responses is an important link to understanding disease,” said Dr. Jones. “It's probably not that a person is exposed to one specific chemical; it's the synergistic effect of a variety of chemicals, and possibly the individual's genetic susceptibility as well.

“We need to look at the complex, interrelated factors that affect cancer rates in certain populations,” Dr. Jones said. “Unless you attack the different sources of the problem, you'll never really resolve it.” ●

For more information, contact Dr. Jones at (713) 792-3316.



Blood and Platelet Donors Give Life

Like ancient Egyptians whose livelihood thrived upon the mineral-rich bounty of the Nile River, the human body depends on the blood flowing through its veins for vitality. So important is blood to human life that the slightest change in it directly affects our health and well-being.

Hospitals depend on blood donations from the community to meet patients' blood transfusion needs. According to blood collection agencies, one unit of blood can save three lives. Accident victims who have lost a lot of blood are not the only people who need blood transfusions – others who may need them include surgical patients, premature babies, bone marrow transplant recipients, and many others. People undergoing chemotherapy for cancer often need blood and platelet transfusions, which is why cancer hospitals are always in need of donations.

What's blood made of?

Blood is made up of four main parts: red blood cells, white blood cells, platelets, and plasma. Red blood cells deliver oxygen from the lungs to the rest of the body and transport carbon dioxide from the body to the lungs. White blood cells fight infection. Platelets combine with other blood components to form clots to prevent bleeding. Plasma, which is 90% water, is the medium in which all the blood components and clotting factors are transported. When you donate blood, it is separated into red blood cells, platelets, and plasma and administered according to specific patient needs.

Why do patients with cancer need so much blood?

Many, if not most, people with cancer undergo chemotherapy, which can temporarily reduce the number of



circulating blood cells. The fatigue most cancer patients experience is caused in part by low levels of red blood cells (anemia), which carry oxygen to muscles. This is particularly true in patients with blood-related cancers such as leukemia, lymphoma, or myeloma, in which the disease itself can dangerously lower the body's production of blood cells. Transfusions of red blood cells are often administered to cancer patients while they recover from the temporary toxic effects of treatment.

Some cancer treatments can also cause a loss of platelets, so platelet transfusions are sometimes given to lower the possibility of a serious bleeding episode in these patients. People undergoing bone marrow transplants, as well as those with leukemia and certain other diseases of the blood, are particularly likely to need platelet transfusions.

How do you donate blood and platelets?

Donating whole blood is a simple process that takes only 30 to 45 minutes from start to finish. Most healthy people between ages 17 and 75, weighing more than 110 pounds, can donate blood. You can donate whole blood as often as every eight weeks. Remember that blood reserves are especially low near holidays and during the summer, when people are busy with other activities, so donations are particularly needed during these times.

Donating platelets is a little more time-consuming (about two-and-a-half hours), but yields five to eight times more platelets than can be collected from a single unit of whole blood. During a platelet donation, small

amounts of blood are taken from the donor's arm and passed through a separator. The platelets are skimmed off, and the other blood components are returned to the donor's body. Because of this, platelet donation shouldn't affect a person's energy level, and can be done as often as every three days, up to 24 times a year.

Is donating blood safe?

Unless the technician has a cold and sneezes on you, you can't get any kind of disease by donating blood or platelets – the completely sterilized and disposable equipment guarantees your safety.

How do I find out more about donating blood?

Call your local cancer center or hospital to find out how you can donate blood or platelets in your community. For more information, visit the American Association of Blood Banks website at www.aabb.org, the American Red Cross website at www.givelife.org, or the Leukemia & Lymphoma Society website at www.lls.org. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

 **(800) 392-1611, Option 3,** within the United States, or

 **(713) 792-3245** in Houston and outside the United States.

January 2005

C. Yeager

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DiaLog

Cancer Pain Control in the New Millennium

Allen W. Burton, M.D.
Section Chief
Cancer Pain Management
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and Pain Medicine

As more and more cancer patients become long-term survivors, an interesting challenge has emerged. Historically, an oncologist's role has been focused on treating the disease itself, but a growing area of concern today is treatment-induced chronic pain in patients whose cancer is considered cured.



Pain and symptom burden remain problematic for many cancer survivors even years after treatment, presenting physicians with a complex pain management challenge. Unrelieved pain adversely impacts the patient's quality of life for many reasons: depression, anxiety, decreased ability to function, and inactivity-related complications such as deep venous thrombosis and pneumonia. Fortunately, as cancer treatment has evolved, so has our ability to enhance people's quality of life at any stage of disease.

Optimum pain control includes the restoration of physical, emotional, and occupational functioning. The treatment regimen may include the judicious use of pharmacologic therapies, physiotherapy, psychological therapy, and at times interventional pain techniques such as neural blockade, neurolytic blocks, percuta-

neous vertebroplasty, or the implantation of a neurostimulator or pain medication infusion pump.

One of the important tools in our arsenal is the spinal administration of analgesics via an implanted pump. This implanted pain pump has been used in the treatment of unrelieved pain of various causes for over a decade, but has recently seen more diverse applications. A growing body of research shows spinal analgesia to be effective in treating many types of chronic, refractory pain, including pain from cancer.

At M. D. Anderson, our pain management group recently published our experience with spinal analgesia (Burton AW, et al. *Pain Med* 2004;5(3): 239-47) and found improved pain control, less requirement for oral pain medications, and importantly, a clearing of mental clouding (presumably related to the lowering of oral analgesic doses). This is concordant with other recent research, reinforcing our recommendation for the use of spinal analgesia in two broad groups of patients: (1) those with refractory severe pain in spite of numerous analgesic regimens and (2) those with mental clouding or other adverse effects of oral analgesics.

In most cases, adequate pain control can be obtained through regular assessment and application of relatively straightforward principles for the use of oral analgesics. In instances of refractory pain, effective treatment can be attained through the thoughtful application of the aforementioned multidisciplinary approach, including the use of spinal analgesia. Such measures will help physicians add quality to their patients' lives as well as quantity.

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