

REPORT TO PHYSICIANS

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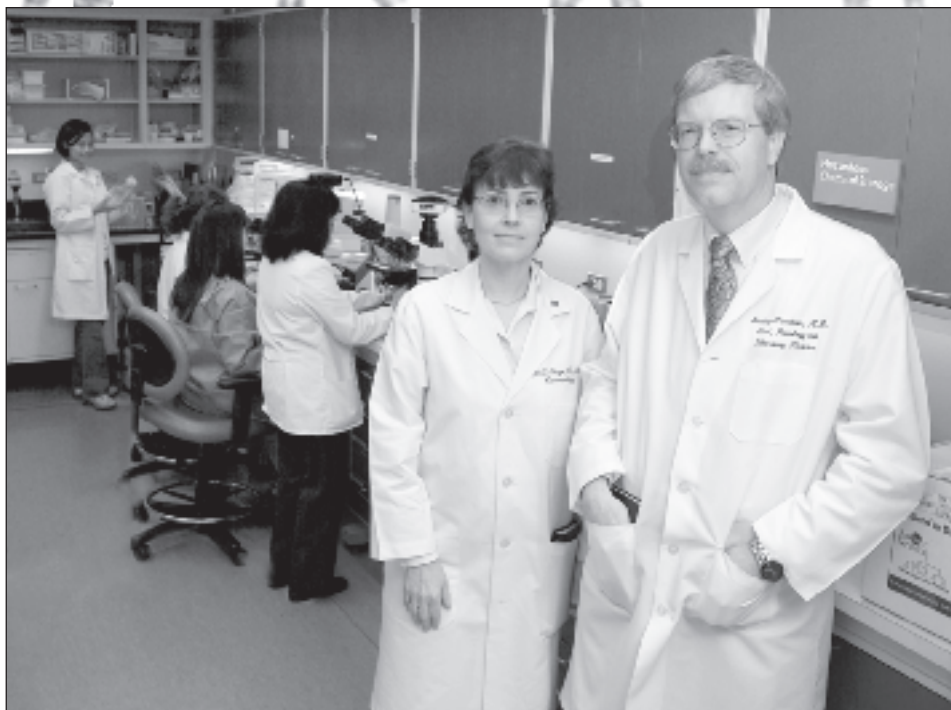
Oncology

Cytogenetics: Major Insights from Microscopic Details

by Beth Notzon

Down a long, quiet hallway, far removed from the daily hubbub of a busy cancer center, is a room full of cytogenetic technologists peering intently through microscopes and studying highly magnified images of chromosomes on computer monitors. They are looking at the body's earliest signposts of cancer, searching for microscopic missteps in the DNA that will offer more insight about the type and course of a particular person's cancer.

With the realization that cancers stem from some kind of genetic defect, many are now being identified by these characteristic defects, explained Stanley R. Hamilton, M.D., a professor and the head of the Division of Pathology and Laboratory Medicine at The University of Texas M. D. Anderson Cancer Center. "Cytogenetics is the science of studying chromosomes themselves as a means of providing a more specific diagnosis and prognosis,"



Chromosomal abnormalities can give doctors more precise information about a patient's disease and its prognosis, say **Dr. Lynne Abruzzo** (l) and **Dr. Stanley Hamilton**.

he said. "A number of cancers have characteristic cytogenetic abnormalities that tell us exactly what kind of cancer we're dealing with."

One example of a genetic abnormality that is seen in virtually every patient with chronic myeloid leukemia is called the Philadelphia chromosome. It results from a translocation between chromosomes 9 and 22. In fact, it is virtually

the hallmark of this cancer. Such information can be the key to a successful outcome because it not only identifies exactly the type of cancer a patient

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Cytogenetics

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has, but also tells clinicians more precisely what the best treatment for a patient should be, how well patients are responding to treatment, and when the disease is recurring—often before it is evident by any other means.

Kimberly Hayes, manager of the cytogenetics laboratory, explained, “When a morphologist looks at cells, the appearance can vary and the findings can be difficult to interpret. In fact, the morphology—the phenotype—can look normal, but the cytogenetics, which looks at the genotype, can be very abnormal, which can help identify relapse in the early stages.” And this, of course, means the treatment of recurrent disease can be instituted earlier, with a better chance of success.

Currently, it is mainly patients with hematologic malignancies—the leukemias and lymphomas—plus patients with sarcoma and certain childhood cancers who benefit the most from cytogenetics. The reasons are simple. One is that the material is easy to get and often plentiful in hematologic diseases. The second is that it is not difficult to grow these cancer cells in cultures. The third is that the genetic abnormalities seen in these cancers are not particularly complex.

The story is different for solid tumors. As Dr. Hamilton explained, “The four big cancers—lung, colorectal, breast, and prostate—are more difficult

Each normal chromosome shows a characteristic banding pattern, and any departure from this banding pattern indicates a genetic abnormality—a deletion, inversion, or translocation.



to work with. First, it's hard to get them to grow in culture. The solid tumors also consist of a mixture of stromal and epithelial cells, so it's difficult to get a pure cancer cell population, and finally, the genetic abnormalities are incredibly complex in most tumors.” Other means are being used, and sought, to get to the root genetic causes of these cancers.

To appreciate why cytogenetics is so valuable, it helps to understand the process cytogeneticists follow. First, the material is obtained; for most cancer

patients, that is usually peripheral blood and bone marrow. After this, the technologists count the cells in a specified volume to determine the sample size needed for cell culture. Next is the critical event that all of cytogenetics hinges on—the cells are cultured in a growth medium for 24 hours or more and then treated with colcemid, which stops cell division and allows the metaphases to be studied more closely.

Then, Giemsa staining of the cells highlights the chromosome bands in a

A Laboratory Mistake Becomes a Miracle

Cytogenetics has actually been around for a long time. In fact, many view cytogenetics as officially having its beginning in 1956, when two researchers first suggested that there might actually be only 46 chromosomes instead of the 48 that had been a commonly held belief for 30 years.

But it wasn't so much this knowledge as how the knowledge was gained that became the seminal event in cytogenetics. It was because, for the first time, researchers had been able to actually see the chromosomes as something other than just a mass of wormlike lines.

The event was even given a name—the “hypotonic miracle.” Actually, according to Kimberly Hayes, it didn't really start out being a miracle. It began with an error—when a technician in the lab of Dr. T.C. Hsu, a world-renowned cytogeneticist, mistakenly poured a salt solution on a specimen, which caused the cells, amazingly and most unexpectedly, to spread apart and the chromosomes to become visible.



Dr. Lian Zhao (l), senior technologist, and **Dr. Lynne Abruzzo** review an abnormal karyotype.

process called GTG (Giemsa Trypsin G) banding. Each normal chromosome shows a characteristic banding pattern, and any departure from this banding pattern indicates a genetic abnormality—a deletion, inversion, or translocation. There can also be a loss or gain of entire chromosomes. Finally, the chromosomes are assembled into a karyotype, which is the grouping of the pairs of chromosomes.

Another technique cytogeneticists use to determine genetic abnormalities is fluorescent in situ hybridization, or FISH. DNA in chromosomes is labeled with a fluorescent probe, and then the cells are viewed under a fluorescent microscope. Though different from cytogenetic analysis, the information FISH yields enhances the karyotype information. In particular, while the karyotype gives overall information about the number and physical appearance of chromosomes, FISH can show whether a gene or mutation specific to a particular cancer is present.

With the increasing demand for cytogenetic information, M. D. Anderson currently has two shifts of cytogenetic technologists, and there's talk of adding a third. And because it has been a challenge to find people with the right set of skills and training to be cancer

cytogenetic technologists, M. D. Anderson has started its own school to train them.

Although cytogenetics and molecular diagnostics have become an increasingly important part of the field of pathology and laboratory medicine, the traditional tools of the specialty will remain an important part of diagnosis and treatment. As Dr. Hamilton explained, "The traditional cytology, pathology, and histopathology will remain a mainstay of diagnosis for decades. The morphology of what we see under the microscope is the end result of all of the genetic and epigenetic abnormalities that occur in cancer cells. These are very cost-effective techniques, and they give us a huge amount of information."

Lynne V. Abruzzo, M.D., Ph.D., an associate professor in the Department of Hematopathology and the chief of the cytogenetics laboratory at M. D. Anderson, pointed out that cytogenetics is such an important tool in the diagnosis and follow-up of patients at the cancer center that the clinicians also "speak the language" of cytogenetics. "It's part of their thinking, and they know how to apply it," said Dr. Abruzzo.

Another benefit of cytogenetics at M. D. Anderson is the effective commu-

A genetic abnormality not only identifies exactly the type of cancer a patient has but also tells clinicians more precisely what the best treatment for a patient should be, how well patients are responding to treatment, and when the disease is recurring.

nication between the different team members—the clinician, the cytogeneticist, the pathologist, the radiologist—who are involved in treating the patient. The information is shared. At weekly leukemia conferences, as Dr. Abruzzo explained, members of the team come together to "look at the flow cytometry results, the cytogenetics results, radiology, pathology, and other findings" and create a complete picture of a patient's cancer that gives them a comprehensive roadmap for treatment. ●

FOR MORE INFORMATION, contact Dr. Hamilton at (713) 792-2040, Dr. Abruzzo at (713) 794-5439, or Ms. Hayes at (713) 792-6330.

Disbelief Guilt Despair Breaking the News Grief Denial



Paying attention to certain aspects of the doctor-patient relationship can reduce the impact of bad news while paving the way for a strong working relationship.

by Rachel Williams

How would you want to get the news of a life-threatening disease? From a voice on the other end of the telephone line or from someone who talks to you in person? In a crowded waiting area or in a private, comfortable office or room? From someone that you barely know or from the health care provider that you have entrusted with your diagnosis and treatment?

These are questions that Estela Beale, M.D., an associate professor in the Department of Psychiatry at M. D. Anderson, suggests physicians ask themselves to remain aware of the psychological and emotional impact with which a diagnosis of cancer slams into a patient's reality. Paying attention to certain aspects of the doctor-patient relationship can reduce the impact of bad news while paving the way for a strong working relationship. When physicians are mindful of their own reactions to the patient and the patient's medical condition, they are better prepared to deliver the news.

"The traumatic effect of a diagnosis of cancer is apparent in most patients," she said. "Even for those who already suspect the possibility of cancer, having that fear confirmed is still traumatic. Different people may respond to the shock in different ways, and physicians should be aware of signs that suggest a patient is having difficulty."

Typical responses

According to Dr. Beale, the most common reaction to a diagnosis of cancer is a state of shock that results in feeling stunned and dazed. The patient and the family tend to feel disbelief about what they hear. People often feel numb for several days. Cognition is affected, making it difficult for the patient to concentrate, understand what is being said, ask questions, or absorb explanations and treatment information being offered by the doctor. Frequently, such patients have trouble sleeping, eating, or handling their normal routines because their minds keep

reliving the diagnosis or because they are consumed with fear about what will happen. For the patient, hearing the diagnosis can be like hearing a death sentence. Physicians should be aware that during this stage, a patient may fail to follow through on instructions or participate in prescribed treatment without additional help and encouragement.

Another reaction, seen more frequently in the elderly, is an apparently calm acceptance. These patients may show no particular shock or surprise and instead seem stoically resigned to the diagnosis. However, underneath a calm exterior there may be a great deal of grief, guilt, or despair.

"Very often the patient is thinking that he caused the cancer as a result of something he did or did not do," stated Dr. Beale. She said that these patients tend to become lethargic, sleep excessively, and sometimes fail to follow treatment plans.

A third reaction, which is more typical in adolescents and young adults, is denial. "These patients develop a need to avoid the reality of cancer altogether and refuse to talk about it or hear the word 'cancer' mentioned in their presence. Their way of dealing with the diagnosis is to pretend the disease does not exist," Dr. Beale stated. "They feel that the only way to remain whole is to stay in control of the information by not allowing discussion or even thoughts about the illness. If it's out of their minds, they can pretend it's not real, and like a nightmare, it will all go away." One problem associated with the denial reaction is a reluctance to go to treatments or follow procedures or even to talk about the subject with anyone. These patients typically have compliance problems.

"It is also normal for people to go through a combination of all three phases to a greater or lesser degree," said Dr. Beale. "Fortunately, most patients, sooner or later, are able to move past the shock of diagnosis and, with time, come to terms with their condition



Dr. Estela Beale encourages physicians to be aware of the emotional and psychological effect a cancer diagnosis can have.

and move in the direction of getting their lives back to normal as much as possible.”

Softening the blow

According to Dr. Beale, there are a few simple things that physicians can do to make a difference in a patient’s ability to handle the initial impact of diagnosis and move past that stage into acceptance and readiness to fight the disease.

- *Remember your importance to the patient.* “First, consider the importance that you, as a health care provider, have in the mind of the patient. To be mindful of that means remembering that the task is not just to convey information, but to do it in a way that takes into account the patient as a whole person.”
- *Give the diagnosis in person.* “Never give a cancer diagnosis over the phone. It is very impersonal and detracts from the doctor-patient

The doctor-patient relationship is very important since it provides the context in which trust, confidence, and hope develop.”

– Dr. Estela Beale

relationship. The doctor-patient relationship is very important since it provides the context in which trust, confidence, and hope develop. Even under the worst medical conditions, a good connection with you gives a patient a sense of security in facing the challenges of the illness and treatment.”

- *Provide a quiet, relaxing environment.* “The room or area in which the diagnosis is given should be as private as possible and have comfortable seating. Certainly, never give

the diagnosis out in a busy hallway or a crowded waiting room.”

- *Take extra time for the diagnostic visit.* “The physician should plan to spend a little extra time with a patient when breaking bad news to allow them to react, ask questions, and absorb the information.” Information should preferably be given in small amounts to give time for reacting, questioning, and assimilating.
- *Let some time lapse between the diagnosis and discussion of treatment options.* “Doctors need to remember that at the time of diagnosis, very often patients only remember about half of what they have been told because they are so frightened and overwhelmed. Once they’ve heard the word ‘cancer,’ everything else you say may be a blur to them, even if they appear to be taking it all in. It may be helpful to schedule a separate session to discuss treatment options and review key information. If that is not possible, provide patients with written information or ask them in advance to bring a supportive friend or relative with them to take notes and serve as a second pair of ears. Some practitioners tape or write down information that was discussed during the session so that patients can go home and review what they have learned.”

No one can protect a patient from the shock of being told, “It’s cancer.” But, as Dr. Beale points out, it really does help the patient cope with and absorb the news more easily if the diagnosis is given under conditions that allow the patient to react as needed. A strong relationship inspires trust and allows the patient freedom to express thoughts and anxieties about the illness or the treatment. ●

FOR MORE INFORMATION, contact Dr. Beale at (713) 792-7546.

Vaccine May Prime the Immune System to Fight Lymphomas

Researchers at M. D. Anderson Cancer Center and the National Cancer Institute have found that an experimental vaccine can prime the immune system to help fight an aggressive form of lymphoma, even if prior therapy has eliminated virtually all of the B cells thought necessary to mount such a defense.

This finding overturns the commonly accepted notion that both B cells and T cells are needed to prime the human immune system.

Their study, published in the September issue of *Nature Medicine*, has important implications for both basic and clinical science, researchers say. It demonstrates that few, if any, B cells are needed to trigger an effective T-cell immune response. This finding overturns the commonly accepted notion that both B cells and T cells are needed to prime the human immune system.

"We were frankly surprised to find that B cells were coming back in patients that were already primed to fight their tumors," said senior author Larry Kwak, M.D., Ph.D., professor and chair of the Department of Lymphoma at M. D. Anderson. "Now we know B cells are not needed for T-cell immunity."

Their research also tests the use of personalized vaccines to help lymphoma patients fend off a recurrence of their cancer after treatment. Several such cancer vaccines are being tested in humans. In this study, conducted at the Center for Cancer Research, National Cancer Institute, treatment with a B-cell depleting treatment regimen followed by an experimental vaccine resulted in an impressive 89% survival rate at 46 months for 26 patients with mantle cell lymphoma, for which there is currently

no effective long-term therapy.

"This is the first human cancer vaccine study to see T-cell responses in the absence of B cells, and this paves the way to use vaccines in a number of hematological cancers that are treated by eliminating diseased B cells," said the study's first author, Sattva Neelapu, M.D., an assistant professor in the Department of Lymphoma.

Testicular Cancer Gene—Of Mice and Men

Researchers have located a gene dubbed "dead end" that, when mutated or lost, causes testicular tumors in mice. They say their study, published in the journal *Nature* on May 19, 2005, may lead to future insights into the genetic causes of the disease in humans because the cancer originates from the same cell type, the primordial germ cell, in both mice and men.

If that notion is validated through further research, the finding could lead to a way to either screen for the human disease or treat it, say the researchers.

"One can envision that this gene or others in its pathway could possibly be used for screening or therapeutic purposes in young males predisposed to develop testicular cancer or those who have a family history of this disease," said the lead investigator, Angabin Matin, Ph.D., an assistant professor in the Department of Molecular Genetics at M. D. Anderson. "This will of course require further research regarding the function of this gene in human cancers."

M. D. Anderson Accelerates Research

M. D. Anderson Cancer Center has unveiled plans for the most aggressive expansion of research in the institution's history, through the establishment of the Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer.

Consisting of six unique centers focused on genomics, proteomics, screening, diagnostic imaging, and biotechnology, the McCombs Institute will be a collaboration between basic and clinical researchers crisscrossing departments, specialties, and disease sites and a magnet for attracting the biotechnology industry to Houston.

The McCombs Institute will bring approximately 750,000 square feet of outpatient care and biomedical research facilities to M. D. Anderson. Approximately 25% of the institution's research activities will be housed within the McCombs Institute.

"The McCombs Institute will bring together some of the world's best laboratory researchers and clinical investigators in the field of cancer. They will be working in disciplines that M. D. Anderson faculty and leadership have identified as promising for the future of cancer research and care," said M. D. Anderson President John Mendelsohn, M.D. "Certainly other institutions have programs that focus on early detection and treatment, but I don't know of any that come close to the size, scope, and level of ambition of the McCombs Institute."

Each of the six centers will be in a separate building, focused on a research topic that transcends departmental lines, and each center brings together basic scientists and clinical researchers from many different disciplines who share a particular research interest. Research already has begun in each center, and construction on the McCombs Institute is expected to be complete in 2008. The six centers are:

- Cancer Metastasis Research Center (Existing),
- Center for Cancer Immunology Research (Completed in 2003),
- Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Molecular Markers (Opening 2005),
- Proton Therapy Center (Opening 2006),
- Center for Advanced Biomedical Imaging Research (Opening 2007–2008), and
- Center for Targeted Therapy (Opening 2007–2008).



From My Bookshelf to Yours

We asked cancer survivors from the Anderson Network to recommend books and other reading materials for someone recently diagnosed with cancer, and here is what they had to say:

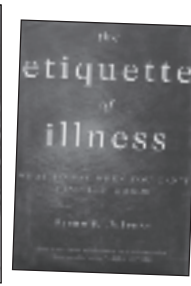
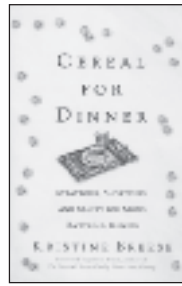
"I highly recommend *Time on Fire* by Evan Handler. Handler shares his experience of dealing with leukemia and navigating a bureaucratic healthcare system with wit, insight, and humor. I also recommend *Cereal for Dinner: Strategies, Shortcuts, and Sanity for Moms Battling Illness* by Kristine Breese and *The Etiquette of Illness—What to Say When You Can't Find the Words* by Susan P. Halpern."

"Here's my list:

- *Bald in the Land of Big Hair: A True Story* by Joni Rodgers,
- *57 Good Things About Chemotherapy* by Alec Kalla,
- *I'd Rather Do Chemo Than Clean Out the Garage: Choosing Laughter Over Tears* by Fran Di Giacomo, and
- *Coping with Chemotherapy* by Nancy Bruning."

"As a breast cancer patient, I found the following to be helpful reading materials:

- the Psalms (Holy Bible),
- *Dr. Susan Love's Breast Book* by Susan Love, M.D.,
- *After Breast Cancer: Answers to the Questions You're Afraid to Ask* by Musa Mayer,
- *100 Questions and Answers About Breast Cancer* by Zora Brown,
- *The Victoria's Secret Catalog Never Stops Coming: And Other Lessons I Learned from Breast Cancer* by Jennie Nash, and
- *Road to Restoration through the Diagnosis of Breast Cancer and Walking on by Faith* by Janice Workcuff."



**Ten minutes
of genuine belly laughter
had an anesthetic effect
and would give me at
least two hours of
pain-free sleep."**

— **Norman Cousins, *Anatomy of an Illness as Perceived by the Patient***

"The day after my cancer diagnosis, my minister came to see me and gave me his copy of *Anatomy of an Illness as Perceived by the Patient* by Norman Cousins, which I would recommend to all patients. Cousins seemingly overcame a highly debilitating illness with, among other things, frequent doses of laughter. He wrote: 'Ten minutes of genuine belly laughter had an anesthetic effect and would give me at least two hours of pain-free sleep.'"

"Here's my list of good reading for patients:

- Any book by Bernie Siegel, M.D., including *How to Live between Office Visits: A Guide to Life, Love and Health*,
- *You Are Not Your Illness: Seven Principles for Meeting the Challenge* by Linda Topf,
- *No Such Thing as a Bad Day* by Hamilton Jordan, and
- The National Cancer Institute Web site (or request reading materials from them), www.cancer.gov."

"One book I read during my treatment is *The Purpose Driven Life* by Rick Warren. That book was very uplifting and helped me to get through difficult days."

"For me, getting all the information I could was my most successful coping mechanism. This resource has both coping and reading materials: www.nci.nih.gov/cancertopics/alphabet."

"I recommend that people start out reading information targeted toward patients, but then move on to detailed information for health care professionals. Since I had melanoma, I also found using a melanoma-specific online bulletin board to correspond with other patients with the same diagnosis was very helpful. I use www.mpip.org/bb/bbindex.html." ●

The Anderson Network is M. D. Anderson Cancer Center's unique support group of more than 1,300 current and former cancer patients. Their patient and caregiver support line is (800) 345-6324.

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.

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DiaLog

Intraperitoneal Chemotherapy: A New Strategy for Advanced Ovarian Cancer

Maurie Markman, M.D.
Vice President for Clinical Research

More than 50 years ago, in the earliest days of the "modern chemotherapeutic" era, oncologists attempted to administer anti-neoplastic agents directly into the peritoneal cavity as treatment for nearby malignancies, including ovarian cancer. However, this strategy was soon abandoned when it was shown that systemic drug delivery produced similar improvement without the local toxic effects, like severe abdominal pain, that were commonly associated with the drugs available for regional treatment at that time.



In the late 1970s, there was renewed interest in intraperitoneal treatment based on theoretical modeling studies showing that malignant cells in the peritoneal cavity could be exposed to much larger concentrations of anticancer agents—10- to 1000-fold greater than with systemic treatment—if direct drug instillation was used.

Multiple phase I and II clinical trials in the 1980s and early 1990s confirmed the safety (e.g., limited abdominal pain), major pharmacokinetic advantage (e.g., 10- to 20-fold for cisplatin; 1000+ fold for paclitaxel), and biological activity (e.g., tumor shrinkage, surgically documented complete responses) of the regional administration of a number of anticancer agents

for ovarian cancer. But while these data were of considerable scientific interest, the trials did not establish the *superiority* of intraperitoneal delivery, compared with standard intravenous drug delivery.

However, over the past decade, the results of three large, multi-institution, randomized phase III trials have now convincingly demonstrated improved survival in advanced ovarian cancer from intraperitoneal delivery. Studies have shown that the intraperitoneal administration of cisplatin, a member of the most important class of agents used in ovarian cancer, results in a statistically significant improvement in both the time to disease progression and in *overall survival* for women with advanced ovarian cancer. The most recently reported trial, conducted by the Gynecologic Oncology Group, revealed a 17-month improvement in median survival associated with this approach compared with intravenous delivery of the cytotoxic agents.

Much remains to be learned about this novel strategy for the management of ovarian cancer, including refining the drugs and dosages and defining the best method of delivery (e.g., types of catheters and the optimal surgical placement technique). Critically important clinical research efforts at many institutions, including M. D. Anderson, will seek to determine the optimal use of this "old," yet highly innovative, management strategy that has now been shown to prolong the lives of women with this very difficult malignancy. ●

OncoLog

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