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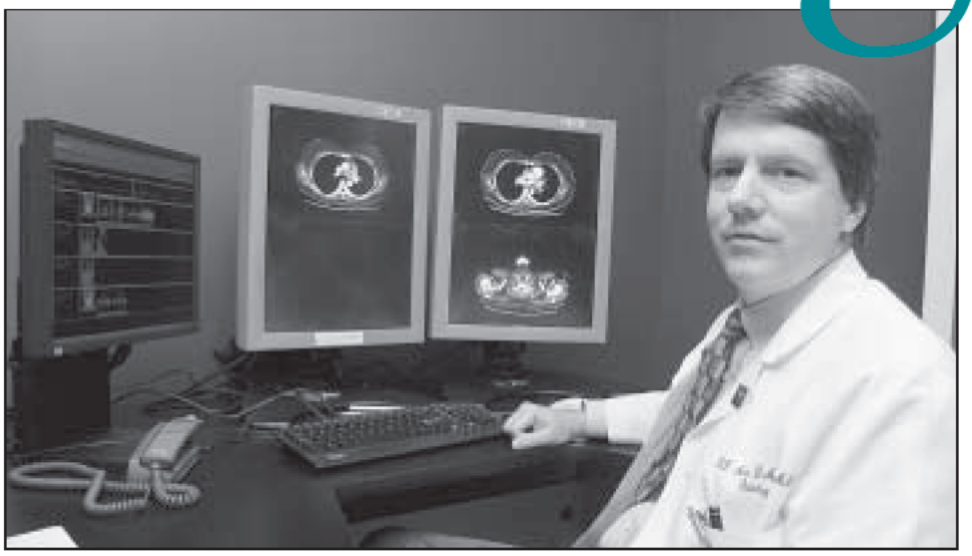
OncoLog

Largest-Ever NCI Trial to Study Lung Cancer Screening

by Dawn Chalaire



Dr. Reginald Munden, *the principal investigator of the National Lung Screening Trial at M. D. Anderson and an associate professor in the Department of Diagnostic Radiology, analyzes computed tomography (CT) scans of lungs.*

Of the four most deadly cancers in the United States, lung cancer is the only one for which screening is not recommended. Although many have questioned the design of the studies of chest x-ray and sputum analysis conducted in the 1970s that led to that conclusion, the National Cancer Institute (NCI) has since found no good evidence that screening can reduce lung cancer mortality rates. Some physicians, however, have continued to screen anyway.

In recent years, spiral computed tomography (CT) has become an alternative to chest x-ray for lung cancer screening. A spiral, or helical, CT scan of the lungs can be taken in a single breath-hold and identify abnormalities as small as 5 mm in diameter, but researchers still do not know if it can find lung tumors early enough to change the outcome of the disease. Some research suggests that the prognosis for patients with 5-mm tumors is no better than that for patients with larger tumors. Many people believe, however, that the smaller a tumor is when it is found, the better the outcome for the patient.

"All of the other successful screening programs—for breast, prostate, and cervical cancers—say that if you find an early cancer, you improve life expectancy," said Reginald Munden, M.D., an associate professor in the Department of Diagnostic Radiology at The University of Texas M. D. Anderson Cancer Center. "We don't know if that's true in lung cancer."

In hopes of answering that question once and for all, the NCI has launched the largest lung cancer screening study ever undertaken. With an enrollment goal of 50,000 participants and a cost of $200 million, the National Lung Screening Trial (NLST) is also the largest and most expensive study of any kind the NCI has ever funded. Participants in the NLST will be recruited from 30 sites across the United States, including M. D. Anderson.

The NLST will measure lung-cancer-specific mortality rates in smokers and former smokers, 55 to 74 years old,

(*Continued on* **next page**)

THE UNIVERSITY OF TEXAS
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Largest-Ever NCI Trial to Study Lung Cancer Screening

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who have been randomly assigned to undergo lung cancer screening with either spiral CT or chest x-ray. The participants will be screened at baseline and then once a year for two years. After the third screening test, they will be followed up with phone and mail surveys for another five to seven years.

"During the design of the trial, many of us argued that the control group should not receive an x-ray. But the reality is that many people are doing chest x-rays to screen, even though it's not recommended, so there was a desire for the study to reflect current practice and a concern that many people would drop out of the trial if they didn't get an x-ray," said Dr. Munden, who is the principal investigator of the NLST at M. D. Anderson.

Participants in the NLST will be screened for free, but any additional tests made necessary by the screening results must be paid for by the participants or their insurance providers. This is an important consideration because spiral CT, although extremely sensitive, lacks specificity and yields a high rate of false-positive results. A lung abnormality found by spiral CT screening requires follow-up testing, which can include a diagnostic CT, positron emission tomography, a lung biopsy, or even surgery.

"So the biggest problem with screening with CT is that we find a lot of abnormalities that aren't significant; however, we don't know that until we spend more money and do more tests, which can be expensive," Dr. Munden said.

The mental anguish that patients must go through while waiting for a diagnosis after having an abnormal result on a screening CT is another consideration. Most important, however, are the physical risks that accompany lung biopsy and surgery. Lung biopsy can result in serious complications, including bleeding, infection, and the partial collapse of a lung.

"So screening is not without risks. Everyone has the perception that the results are either negative or positive, but it is not that crystal clear," said Dr. Munden. "The results that are truly negative and the ones that are almost certainly cancer, those are easy. But everything that is in between—perhaps in as many as 70% of our participants—those are the ones you have to deal with, and it can be complicated."

In fact, an important component in the development of the NLST was an attempt to address the difficulties inherent in reading screening CT scans of the lungs. The American College of Radiology Imaging Network (ACRIN) submitted a proposal to the NCI for a lung cancer screening trial that included a focus on the technical aspects of CT screening and the interpretation of CT scans. At about the same time, another group, the network conducting the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, submitted a separate lung cancer screening proposal to the NCI, which merged the two proposals into one large, comprehensive trial, the NLST.

The ACRIN study sites, which include M. D. Anderson, are conducting additional tests to measure quality of life, smoking cessation, and smoking addiction. Also, M. D. Anderson is one of 10 sites at which researchers are asking participants to allow them to collect samples of blood, urine, and sputum for use in future studies of lung cancer biomarkers.

"The hope is that in the people in whom we find lung cancer, we can go back and look at their samples to see if there is something different in their genetic markers from the other group," said Dr. Munden. Identifying genetic changes that place people at higher risk for lung cancer could help researchers decide who should be screened for lung cancer and at what age.

When the NLST opened in September 2002, centers were given two years to enroll participants. Recently, however, in an effort to obtain results as quickly as possible, the NCI shortened the recruitment deadline to one year, which has left many centers scrambling to meet their recruitment goals.

To help spread the word about the NLST, the NCI has teamed up with the American Cancer Society (ACS), which has donated money and other resources to recruit participants for the NLST.

Dr. Therese Bevers, *an assistant professor in the Department of Clinical Cancer Prevention, is co-principal investigator of the NLST at M. D. Anderson.*

"I think it's a very exciting collaboration," said Therese Bevers, M.D., an assistant professor in the Department of Clinical Cancer Prevention and co-principal investigator in the NLST.

According to Dr. Bevers, the partnership with the ACS opens doors that allow her to reach many more people than would be possible otherwise. "It is the first time that there has been a collaboration between the ACS and a large-scale prevention trial to recruit participants. And what I think is so wonderful about that is the ACS has a fabulous grassroots network in the community and a way of filtering and getting that information out to the people that I wouldn't have, that the NCI wouldn't have," she said.

The ACS is distributing information about the NLST through fundraising events such as the Relay For Life and through its corporate connections. ●

FOR MORE INFORMATION, *contact Dr. Munden at (713) 792-5885 or Dr. Bevers at (713) 745-8048. Those interested in participating in the NLST may call (866) 295-3386 (toll free) or (713) 792-5340.*

The American Cancer Society offers a free counseling service called Quitline to people who are trying to stop smoking. The Quitline toll-free number is (877) YES-QUIT ([877] 937-7848).

"What Choices Do I Have?"

Breast Reconstruction Book and CD-ROM Help Patients Make Complicated Decisions

by Sunni Hosemann and Kate Ó Súilleabháin

A woman diagnosed with breast cancer today has a far better chance of being cured than her grandmother or even her mother had. Still, in most cases, having breast cancer means undergoing surgery, and surgery leaves scars, both physical and psychological. Restoring the missing form of a woman's breast after mastectomy can be an important step in her recovery, often signaling the end of the cancer treatment and the return to a normal life.

The many treatment and reconstructive options available to women today can make decisions about breast reconstruction surgery complicated, however. Should the patient choose a breast implant or an autologous tissue transplant? If she opts for autologous reconstruction, what type of tissue flap should be used?

To educate patients about their options for breast reconstruction, the Department of Plastic Surgery at The University of Texas M. D. Anderson Cancer Center recently released two resources: a CD-ROM and a full-length book. Both the CD-ROM and the book provide complete information in useful formats that patients can explore on their own time, guiding women through the maze of information that is vital for making the important choices about breast reconstruction.

Informing patients fully of their breast reconstruction options is challenging, in part because the consultation with the plastic surgeon usually takes place when the patient is already overwhelmed with information about her cancer treatment.

"There is a lot of material to cover in a short period of time," said Gregory P. Reece, M.D., a professor in the Department of Plastic Surgery at M. D. Anderson and editor of the book *The Well-Informed Patient's Guide to Breast Reconstruction*.

Breast reconstruction is secondary to eradicating the cancer but should not be considered an afterthought. In fact, decisions about breast reconstruction should be made early, as a woman's preferences about reconstruction can influence her treatment choices and vice versa. Some breast tumors, for example, may be treated with a partial mastectomy (lumpectomy) followed by radiation therapy rather than by simple mastectomy. Without having considered reconstruction, many women would choose to undergo the less extensive lumpectomy, but depending on the size of the breast, the size of the tumor, and the woman's preferred outcome, mastectomy might be the better choice to ensure the best aesthetic results.

The timing of reconstructive surgery can affect the results of breast reconstruction. Many women can undergo immediate reconstruction, which is performed at the same time as the mastectomy. This approach allows the plastic surgeon to work with the general surgeon to perform a skin-sparing mastectomy that can enhance the appearance of the reconstructed breast. But aesthetics are not the only consideration. Many women wish to wake up after mastectomy with their new breast already reconstructed, whereas others choose to separate the cancer treatment and the reconstruction process.

The CD-ROM program, *Breast Reconstruction: What You Need to Know*, was spearheaded by Michael J. Miller, M.D., a professor in the Department of Plastic Surgery, and produced by UT Television. The program contains video and animated illustrations, as well as a feature that allows the user to print text transcripts. Physicians and other healthcare professionals from the Department of Plastic Surgery and the Nellie B. Connally Breast Center at M. D. Anderson deliver medical information, but the program also features women

(Continued on **page 4***)*

"For many women, reconstruction is part of recovery from breast cancer," said **Dr. Michael J. Miller**, *a professor in the Department of Plastic Surgery. Here, Dr. Miller looks at the CD-ROM program* Breast Reconstruction: What You Need to Know.

Educating Patients about Breast Reconstruction

(Continued from **page 3***)*

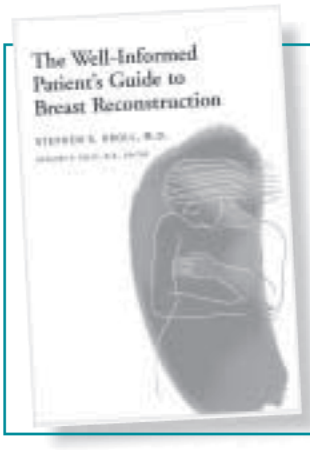
who have personally faced decisions about breast reconstruction.

Fifteen former patients were involved in the CD-ROM's development, beginning with its basic concept. The group met to review the program's content and scripts, offering suggestions and changes of wording along the way. "They came up with additions to the content that no one would have thought of, except a woman who's been there," Dr. Miller said.

One of these women was [redacted], who underwent breast cancer treatment and reconstruction several years ago. [redacted], a volunteer in the Plastic Surgery Center at M. D. Anderson, realized how important it was for women to be able to talk with someone who had been in the same situation, and she was very much aware of how newly diagnosed patients feel: overwhelmed.

"No matter how much time the physician spends with you, you cannot absorb it all at once," she said. "You feel so powerless against a powerful disease. The information gives some of the power back by helping you be more confident about your decisions."

The CD-ROM's introductory section, "First questions," gives an overview of how and when breast reconstruction can be done, how the procedure might interact with cancer treatments such as chemotherapy and radiation therapy, and whether the surgery has any bearing on cancer recurrence. The series of videos in the second section, "Tell me more," describes breast reconstruction using implants, a TRAM flap, and a latissimus dorsi flap (three of the most common techniques), as well as how the nipple can be reconstructed. Animation, illustrations, and sets of before-and-after photographs are complemented by features on women who have undergone reconstruction. In the last section, "Help me decide," patients explain how they chose their method of breast reconstruction and how they feel about the results. The section also outlines the advantages and disadvantages of each technique and provides a useful table to help patients make decisions based on their circumstances, body type, and primary goals.



Dr. Gregory P. Reece *(pictured), a professor in the Department of Plastic Surgery, edited the book* The Well-Informed Patient's Guide to Breast Reconstruction, *which was written by the late* **Dr. Stephen S. Kroll**, *a pioneer in breast and nipple reconstruction.*

The Well-Informed Patient's Guide to Breast Reconstruction was written by Stephen S. Kroll, M.D., a professor of plastic surgery at M. D. Anderson who died in 2000. According to his friend and longtime colleague Dr. Reece, who edited the book and prepared it for publication, Dr. Kroll was well known for his innovations in breast and nipple reconstruction. "He did a lot of breast reconstructions and helped push the envelope for various techniques," Dr. Reece said.

Dr. Kroll had intended the book as a comprehensive resource to educate women on all aspects of breast reconstruction and to reinforce the information conveyed during consultations. Whereas the CD-ROM is distinguished by patient profiles and a unique audiovisual format, the book provides the rare insight of a renowned plastic surgeon in a full-length volume written for a lay audience. Having consulted with hundreds of women on breast reconstruction, Dr. Kroll included answers to the wide-ranging questions that arose during his 18 years as a plastic surgeon.

"I think that a well-informed patient is ultimately going to be more satisfied at the end," said Dr. Reece. "One of the things I hate hearing a patient say is, 'Had I known [about a certain aspect of a technique], I would not have picked this particular form of reconstruction.'"

The Well-Informed Patient's Guide to Breast Reconstruction describes breast reconstruction techniques in detail and includes medical illustrations showing how each procedure is done, along with before-and-after photographs of patients. Included are explanations of the risks, benefits, recovery times, and range of aesthetic outcomes associated with each method. In addition to the three most common techniques described in the CD-ROM program, the book describes several alternative techniques of breast reconstruction that are available at some of the larger cancer centers, such as using flaps made from tissue from the buttock or hip. Incidences of failure and complications, as reported in the medical literature, are included to help the reader fully understand the pros and cons of each method and to put these risks into context. Several techniques of nipple reconstruction are described, as are procedures to match the opposite breast and to revise the reconstruction to achieve symmetry, always the fundamental goal of breast reconstruction. The text also guides readers on practical matters such as economic and insurance issues, choosing a plastic surgeon, and even preparing the patient's home to ensure her maximum comfort after the surgery.

"I think the book and the CD are complementary," Dr. Reece said. "The CD gives . . . more of an overview and gives some personal aspects of patient point of view, whereas in the book, I think we go into the details quite a bit." ●

To order a copy of the CD-ROM Breast Reconstruction: What You Need to Know *in English or Spanish, visit the following Web site: www.mdanderson.org/breastreconstruction.* The Well-Informed Patient's Guide to Breast Reconstruction *is also available on the Web, at www.mdanderson.org/breastreconstructionbook.*

HOUSE•CALL

Coping with the Adverse Effects of Cancer Treatment

Cancer treatment can be a bitter pill to swallow: the harmful side effects, called adverse effects, are sometimes worse than the disease. Treatments like chemotherapy and radiotherapy are designed to kill rapidly growing cancer cells, but they also kill many healthy cells, especially in the bone marrow, digestive tract, reproductive system, and hair follicles. The death of these healthy cells is what causes adverse effects.

Although a lot of progress has been made in preventing and treating the adverse effects of cancer treatment, many patients still experience them. Below are some of the most common physical adverse effects of cancer treatment and suggestions for helping patients cope with them.

Fatigue

Fatigue is the most common adverse effect of cancer treatment; about 90% of patients receiving treatment for cancer have fatigue. It is also the most distressing symptom for many patients. Rest does not always relieve cancer-related fatigue, which is usually more severe and persistent than normal fatigue. There is no cure for this kind of fatigue, but it can often be managed by taking the following steps:

- Take short naps or breaks throughout the day.
- Take short walks or do other light exercises.
- Drink plenty of fluids and eat as well as possible.
- Limit the intake of caffeine and alcohol.
- Save energy for the most important things; ask friends and family for help with difficult tasks.

Nausea and vomiting

Many patients fear the nausea and vomiting that may accompany cancer treatment. Fortunately, antiemetics and antinausea drugs have become very effective in preventing these symptoms. However, no medicine works for everyone 100% of the time. The patient should continue to work with his or her doctor to find the right medication, but in the meantime, these tips may bring some relief:

Eat as well as possible!

- Eat and drink slowly.
- Eat small meals throughout the day instead of three big meals.
- Breathe slowly and deeply or use relaxation techniques such as self-hypnosis, biofeedback, and guided imagery when nauseated.
- Avoid sweet, fatty, spicy, or fried foods as well as bothersome odors.
- Wear loose-fitting clothes and try to stay in a well-ventilated area.

Infection

Most cancer treatments increase a person's risk of getting infections, which are often caused by the patient's own bacteria found on the skin and in the mouth, intestines, and genital tract. Good hygiene will help prevent many infections. Patients with cancer should take the following precautions:

- Wash hands often, especially before eating, after using the bathroom, and after touching animals.
- Stay away from people who have a cold, the flu, or any other contagious illness.
- Be careful to avoid cuts. Use an electric shaver.
- Avoid immunizations without checking with the doctor first, and avoid people who have recently received "live virus" vaccinations, such as those for smallpox and chicken pox.
- Avoid contact with raw fish, seafood, meat, or eggs.

Poor appetite

Eating well during cancer treatment is important because patients need to consume enough calories to maintain a healthy weight and enough protein to rebuild tissues. Proper nutrition helps patients to heal, cope with the adverse effects of treatment, and fight infections. Unfortunately, some cancer treatments cause people to lose their appetites. To get the balanced diet they need to fight their illness, patients with cancer are encouraged to do the following:

- Eat frequent, small meals or snacks whenever hungry.
- Drink beverages and eat soup when solid foods are unappealing.
- Vary the diet and mealtime routine by trying new foods and recipes and eating in different locations.
- Take a walk before meals to increase hunger.
- Ask friends and family for help with grocery shopping and cooking.

Patients should tell their health-care providers if they are experiencing any of the symptoms described above. Often, medicines and palliative techniques can effectively treat the adverse effects of cancer treatments. Above all, remember that healthy cells usually mend when the treatments are finished and that most symptoms will subside in time. ●

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

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

(713) 792-6161 *in Houston and outside the United States.*

June 2003

The new 85,000-square-foot **Proton Therapy Center at M. D. Anderson**, *which will open in 2006, will include four treatment rooms, dedicated research space, a clinic, office space, and treatment-planning stations.*

New Proton Therapy Center to Deliver Radiation with Precision, Few Side Effects

by Kerry L. Wright and Dawn Chalaire

Construction of a much-anticipated 85,000-square-foot Proton Therapy Center at The University of Texas M. D. Anderson Cancer Center officially began on May 7 as representatives from M. D. Anderson and private investors attended a ground-breaking ceremony for the new facility, which will take three years and approximately $125 million to build. When it is completed, the center will join two existing hospital-based proton therapy centers operating in the United States and be the largest of its kind in the world.

The advantage of proton therapy over traditional radiation treatments is that it is more precise in its delivery of radiation dose to the targeted tumor, avoiding many of the surrounding tissues, causing fewer side effects, improving tumor control, and increasing survival rates, said James D. Cox, M.D., professor and head of the Division of Radiation Oncology at M. D. Anderson.

The photons or electrons used in conventional radiation therapy deposit most of their energy in the tissues they pass through before reaching the tumor and often deliver radiation beyond the targeted tumor to surrounding normal, healthy tissue. Although advanced techniques such as intensity-modulated radiation therapy can reduce the exposure of healthy tissue to radiation, with photon radiation therapy, the delivery of at least a small amount of radiation to these structures cannot be avoided.

"So we are often limited in the radiation dose we can give to the tumor because we are limited by the radiation tolerance of the normal tissue surrounding the tumor," said Dr. Cox.

Protons, in contrast, work in an essentially reverse manner, entering the body at a low dose that increases when the beam, directed by a radiation oncologist, nears its target, said Dr. Cox. The largest dose is then deposited in the tumor site, and the proton beams stop there rather than continuing through the body. "Protons kill cancer cells very much like x-rays, but they can be aimed with such precision as to concentrate the cancer-killing effects only within the tumor," Dr. Cox said. "We will be able to focus energy like we never have before."

Protons are energized to specific velocities, and these energies determine how deeply in the body the protons will deposit their maximum energy. Since proton beams are heavier than their conventional counterparts, they can be delivered more precisely and prescribed to cover the entire tumor. The result: proton beams can treat tumors deep within the body while producing minimal or no side effects in surrounding tissues.

"So now, instead of asking what the normal tissue tolerance is when you irradiate a tumor, proton therapy allows you to ask what amount of harmful radiation is actually needed to destroy the tumor," said Mitch Latinkic, division administrator for the Division of Radiation Oncology. Latinkic came to M. D. Anderson after participating in the establishment of the first hospital-based proton therapy center in the United States at Loma Linda University Medical Center in California, which treated its first patient in 1990.

M. D. Anderson is aiming to open its center in the early part of 2006. The new facility will house four treatment rooms, three of which will be equipped with rotating gantries 35 feet in diameter and weighing almost 200 tons each that are capable of directing proton beams with submillimeter precision. One of these rooms will be designed to deliver intensity-modulated proton therapy, what Dr. Cox referred to as "the ultimate" in proton beam shaping. "There is nothing that we can envision that is going to be more precise," he said.

The fourth treatment room will house two stationary beamlines. One beamline is designed to administer specialized

fixed-beam treatments, such as those used to treat certain ocular conditions. The second beamline will also have a fixed beam for treating cancers that require proton beams from a limited number of directions, including brain, head and neck, and prostate cancers.

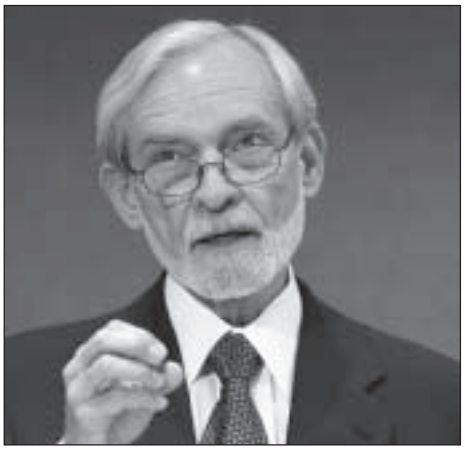
Additionally, the center will contain a separate room dedicated to research, as well as clinic and office space and treatment-planning stations. It is anticipated that more than 3,000 patients with cancer will be treated in the new center each year.

Powering the proton therapy treatments will be a high-energy synchrotron, a compact particle accelerator that emits proton beams of different energies. The synchrotron and related proton beam therapy equipment will be provided by Hitachi. Other partners in the project include the Houston-based financial services firm Sanders Morris Harris, Inc.; The Styles Company, a health-care management and development firm; the Houston Firefighters' Relief and Retirement Fund; the Houston Police Officers' Pension System; General Electric; Varian Medical Systems; and IMPAC Medical Systems.

"This creates a unique relationship that partners academic medicine with the private sector," said Latinkic. While M. D. Anderson will be fully responsible for operating, staffing, and clinically directing the center, the investors will provide the necessary capital and participate in the development of the facility. According to Latinkic, the center will also have a strong commitment to clinical research, as well as to the advancement of proton therapy research and development.

"We are going to develop collaborative investigations with a small number of proton facilities around the world," said Dr. Cox. As part of the Proton Therapy Cooperative Oncology Group, M. D. Anderson will work with colleagues at Loma Linda University Medical Center, Massachusetts General Hospital, and other facilities around the world to conduct clinical trials of proton therapy for different tumor sites.

Much of the cancer research being conducted today is focused on biological approaches to treating cancer, including gene therapy and molecular targeting. Once these approaches are available internationally, Dr. Cox hopes that the cooperative group can study them in combination with proton therapy and standard chemotherapy. Such combination therapies will be particularly important for sites like the lung, which is very sensitive to radiation and difficult to treat with standard therapies. Proton therapy will be used in conjunction with conventional radiation therapy, chemotherapy, and surgery. According to Dr. Cox, it will also have a big impact in children, where the late effects of conventional radiation therapy can surface decades after initial treatment and for whom the trend of late has been to replace radiation therapy with other treatment options.



Dr. James D. Cox, *professor and head of the Division of Radiation Oncology, speaks at the groundbreaking ceremony for the new Proton Therapy Center.*

Although the precision of proton beam therapy has been known for decades, applications were initially limited to a few anatomic sites because accelerators were not designed for treating patients and because many tumors could not be visualized with sufficient precision. Beginning in the late 1970s, imaging modalities, including computed tomography, magnetic resonance imaging, and positron emission tomography, greatly advanced the diagnosis and visualization of cancerous tumors, thus giving physicians the ability to precisely map the location of tumors and making proton therapy more practical.

More than 33,000 patients with cancer have already been treated with proton radiation therapy, and this number is expected to increase dramatically in the coming years as M. D. Anderson's Proton Therapy Center becomes operational and the full impact of this therapy and its applications are realized. ●

FOR MORE INFORMATION, *contact Dr. Cox at (713) 792-3411 or Mitch Latinkic at (713) 794-4720.*

How Proton Therapy Works

- At the beginning of the process, which is measured in fractions of a second, the proton begins its journey within an electric field. In the field, hydrogen atoms are separated into electrons and protons.
- Protons are then sent through a vacuum tube into a linear accelerator or preaccelerator, where their energy is boosted to seven million electron volts.
- Proton beams stay in the vacuum tube as they enter the synchrotron, where they are accelerated, increasing their energy to a total of 70 to 250 million electron volts, enough to place them at any depth within the patient's body.
- After leaving the synchrotron, the protons move through a beam-transport system made up of a series of magnets that shape, focus, and direct the proton beam to the appropriate treatment room.
- Each treatment room has a guidance system to direct the beam that treats the patient. This system will monitor the proton beam until it enters the patient and position the beam to conform to the shape and size of the tumor, according to a plan designed by the physician.
- The beam delivery system, or nozzle, is the last device the protons travel through before entering the patient's body. The nozzle shapes and spreads out the proton beam in three dimensions.
- The entire proton therapy facility is controlled by a network of computers that are equipped with appropriate safety measures to ensure that each patient receives the prescribed treatments and that the entire proton beam therapy system operates safely and efficiently. ●

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Treating Breast Cancer with Hormone Therapy: Past, Present, and Future

Daniel J. Booser, M.D., F.R.C.P.C.
Associate Professor, Department of Breast Medical Oncology

Physicians have been treating breast cancers with hormone therapy since 1896, when Beatson described the improvement of women with metastatic breast cancer after their ovaries were removed.

Tamoxifen, a selective estrogen receptor modulator (SERM), is effective regardless of menopausal status. Overexpression of the estrogen and progesterone receptors (ER and PR) is a reasonably good predictor of its benefit.

Tamoxifen is the only SERM approved for adjuvant and metastatic treatment of breast cancer and for risk reduction in women at high risk. It reduces the risk of recurrence for women potentially cured of receptor-positive breast cancer and reduces the risk of a new breast cancer in women taking adjuvant treatment. Tamoxifen also reduces the early incidence of receptor-positive cancer. This is widely promoted as preventing breast cancer, but delayed disease manifestation seems more likely.

The only treatment indication for raloxifene, another SERM, is postmenopausal osteoporosis; it should not be prescribed as a "designer estrogen." The Study of Tamoxifen and Raloxifene (STAR) trial is comparing the risk-reduction potential of raloxifene with that of tamoxifen in women at high risk (≥ 1.67% in five years) for a first breast cancer.

The reversible aromatase inhibitors anastrozole and letrozole are at least as effective as tamoxifen in the initial treatment of postmenopausal women with metastatic breast cancer, and they are frequently beneficial after relapse on tamoxifen. The irreversible aromatase inactivator exemestane may prove to be even more effective. Tamoxifen's lasting benefit and safety, however, make many reluctant to switch to adjuvant anastrozole without long-term evidence.

Leuprolide and goserelin are luteinizing hormone–releasing hormone agonists used to treat premenopausal women with metastatic breast cancer, and they may provide additional clinical benefit when given with tamoxifen. Fulvestrant, the most recent hormonal agent, destroys the estrogen receptor. Its place in the sequence of treatments has not been determined.

Hormonal treatment is almost always ineffective against tumors lacking ER and PR. However, many tumors overexpressing these receptors do not respond. The original estrogen receptor, now called ERα, differs in function and tissue distribution from the recently described ERβ. These bind to more than 20 coregulator proteins and may act indirectly through other transcription factors. SERMs have a variable influence on these factors, and endogenous estrogen levels may affect the sensitivity of the target tissue to a particular drug. A better understanding of the molecular changes in biochemical pathways associated with ER and PR should lead to more effective hormonal treatments for breast cancer.

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