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REPORT TO PHYSICIANS

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OncoLog

Dr. Jeffrey Weinberg *in M. D. Anderson's new BrainSUITE, which will open in summer 2006.*

A Better Kind of Brain Surgery

A high-tech operating room featuring sophisticated imaging technology helps neurosurgeons more precisely and safely extract complex brain tumors.

by Sunni Hosemann
with reporting by Dawn Chalaire and Dianne Witter

The human brain is an especially bad place for a tumor. Surgically navigating this vulnerable terrain, completely removing a tumor, and leaving without damaging key structures only a few millimeters away requires extraordinary precision and skill.

An extremely high-tech road map doesn't hurt, either.

Such is the thinking behind BrainSUITE, M. D. Anderson's new, $9.2 million system of advanced imaging technologies brought together in a sophisticated new operating room. The equipment is designed to give surgeons better information intraoperatively to help them completely and safely remove complex, hard-to-access brain tumors, with advanced surgical and diagnostic tools combined in one room.

"Precision in resection is key because survival in patients with brain tumors parallels the percentage of tumor successfully resected," points out

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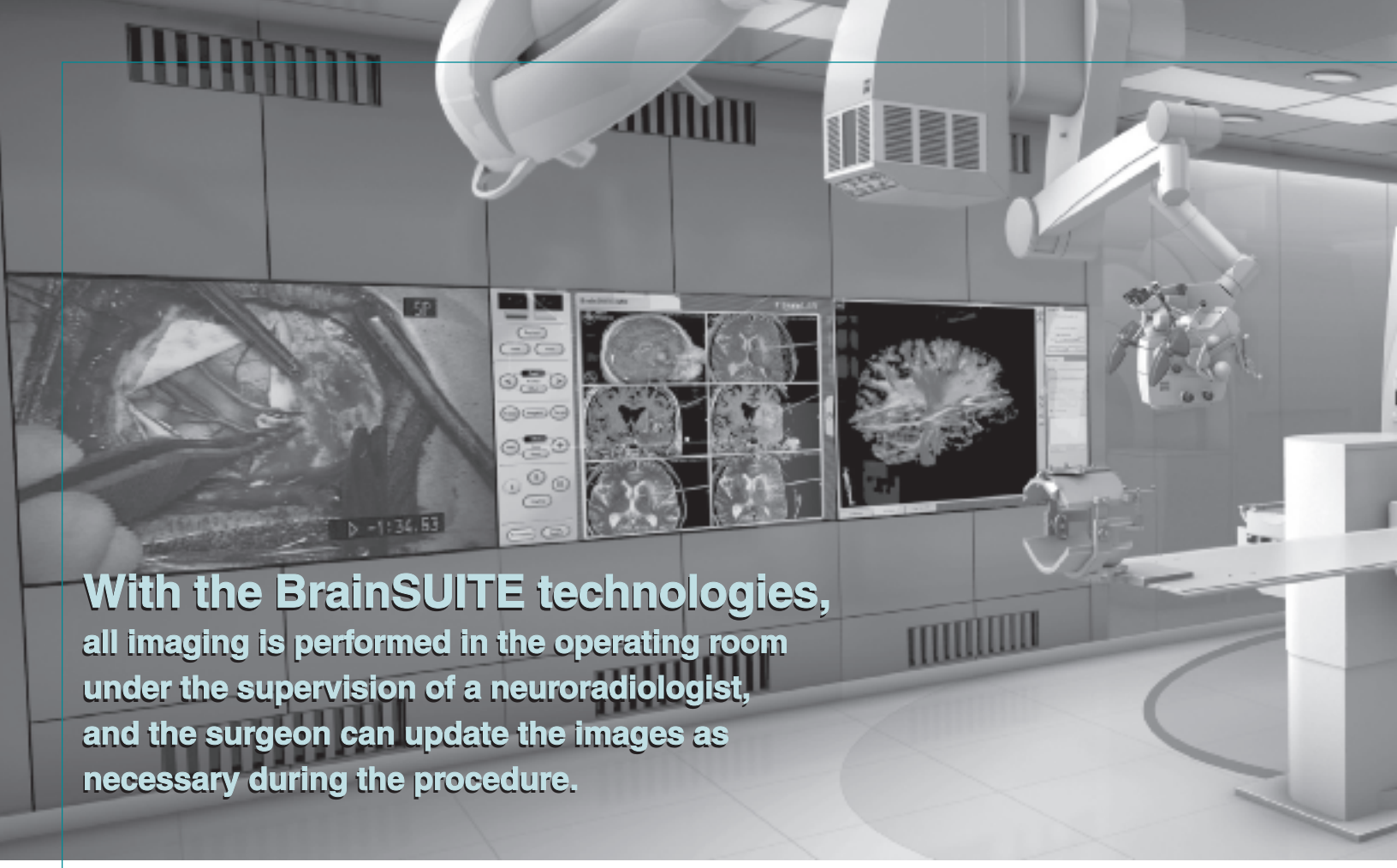


With the BrainSUITE technologies, all imaging is performed in the operating room under the supervision of a neuroradiologist, and the surgeon can update the images as necessary during the procedure.

Raymond Sawaya, M.D., a professor and chair of the Department of Neurosurgery at The University of Texas M. D. Anderson Cancer Center. "Even among patients with glioblastoma, the most malignant of brain tumors, we see a subset of these patients still alive 7 or 8 years later—these are patients whose resection was complete."

An image-guided surgical system

The BrainSUITE is anchored by two core pieces of equipment: a high-intensity intraoperative wide-bore magnetic resonance imaging (MRI) scanner and an integrated image-guided surgical system. The new 1.5-Tesla MRI scanner is more powerful than previous intraoperative MRI magnets of 0.2 Tesla in magnetic strength. Its special wide-bore opening will accommodate a patient placed on his or her side, whereas most scanners require the patient to be lying flat. Therefore, a patient who has a brain tumor that must be accessed from the side of the head, which is inaccessible in most other intraoperative MRIs, can now undergo surgery in the BrainSUITE. These features, along with a special pivoting operating table, allow for scanning to be done periodically during surgery with minimal intrusion, providing the surgeon with much more accurate and up-to-date information during the procedure.

"Precision in resection is key."

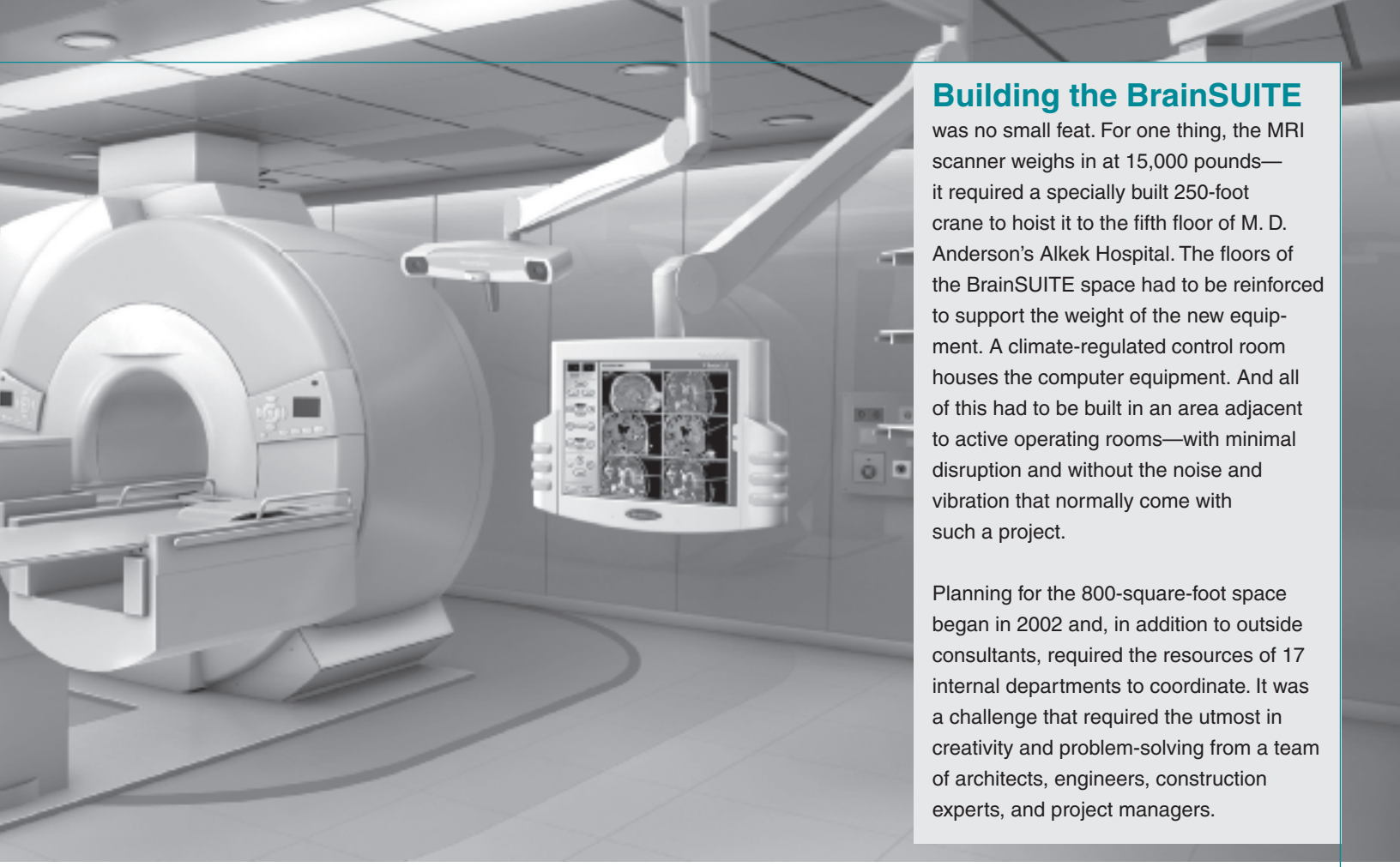
– Dr. Raymond Sawaya

The image-guided surgical system of ceiling-mounted cameras and fiberoptic wiring incorporated in the BrainSUITE provides the surgeon with continually updated images on huge monitoring screens during the procedure. This is important because the surgical field changes during surgery: when tumor tissue is removed, the remaining tissue shifts.

According to Dr. Sawaya, this movement of tissue within the surgical field isn't a problem in many kinds of surgical procedures, but during brain surgery—particularly surgery for large, deep tumors—it can be significantly disorienting for the surgeon.

According to Jeffrey Weinberg, M.D., an assistant professor in the Department of Neurosurgery and the medical director of the BrainSUITE, besides ultrasound, other methods currently used for image guidance during brain surgery do not account for that shift. Instead, surgeons rely on a preoperative MRI and use ultrasonography intraoperatively.

Typically in brain surgery, radiologic markers are placed on the patient's forehead the day before surgery, and the patient undergoes a preoperative MRI scan. In the operating room on the day of surgery, after the induction of anesthesia, the head is fixed in place, and the markers are registered to the preoperative image. During the procedure, the surgeon compares his or her impression of the operative field with



Building the BrainSUITE

was no small feat. For one thing, the MRI scanner weighs in at 15,000 pounds—it required a specially built 250-foot crane to hoist it to the fifth floor of M. D. Anderson's Alkek Hospital. The floors of the BrainSUITE space had to be reinforced to support the weight of the new equipment. A climate-regulated control room houses the computer equipment. And all of this had to be built in an area adjacent to active operating rooms—with minimal disruption and without the noise and vibration that normally come with such a project.

Planning for the 800-square-foot space began in 2002 and, in addition to outside consultants, required the resources of 17 internal departments to coordinate. It was a challenge that required the utmost in creativity and problem-solving from a team of architects, engineers, construction experts, and project managers.

the preoperative image from the day before to make judgments about shift, about the extent of tumor removed, and about the location of critical structures that sit only millimeters away.

"Now, with the BrainSUITE, our surgeons will have coordinated access to more real-time information more quickly than ever before and that will translate into better patient outcomes," Dr. Sawaya added.

The magnetic field

One unique challenge of doing surgery in the BrainSUITE is working near a powerful magnetic field. A 1.5-Tesla MRI scanner, such as the one in the BrainSUITE, contains a magnet so strong that objects drawn to it can become dangerous projectiles. Surgeons, neuroanesthesiologists, and others caring for patients in the BrainSUITE must ensure that the equipment they use is compatible with the MRI or out of range of its strong magnetic force. Patients are prescreened for any metallic objects or implants that might be attracted to the magnet as well.

"Everything that we normally tell people not to do in the MRI environment, we are going to do in the BrainSUITE, including bringing in equipment and surgical instruments that contain ferrous material," said David Ferson, M.D., who heads the Section of Neuroanesthesia at M. D. Anderson. "However, the key is not to allow any of these objects to come close to or cross the 5-Gauss line, at which point they could become projectiles. This will require tremendous coordination, attention to detail, and teamwork by all the operating room personnel."

Safety and accuracy

The BrainSUITE's design will allow neurosurgeons to remove brain tumors more safely than ever before because the MRI scans will enable surgeons to more precisely locate—and circumnavigate—critical structures of the brain like the optic nerve and the brain stem. "This will reduce the possibility of neurological deficit that can negatively impact a patient's quality of life after surgery," said Dr. Weinberg.

With BrainSUITE technologies, surgeons, patients, and families anxiously waiting for information don't have to wait for postoperative imaging to learn whether the tumor was successfully removed. Since all imaging is performed in the operating room under the supervision of a neuroradiologist, the surgeon has information about the procedure's success right away. Because there is no waiting to learn if the tumor was completely resected, the number of repeat surgeries, with their attendant risks and costs, is expected to decline.

Not every patient needs the sophisticated technology afforded by the BrainSUITE, but "it's important for an institution like M. D. Anderson to have this capability," Dr. Weinberg said. At M. D. Anderson, almost 1,000 brain tumor surgeries are performed every year—more than at any other hospital in the nation. And for the most part, those surgeries involve large, deep tumors that represent a high degree of complexity. Even among M. D. Anderson patients with brain tumors, Dr. Weinberg estimates that only about half will require surgery in the BrainSUITE.

For those that do, however, a surgeon can emerge from surgery to meet the family with more than a guess about how much of the tumor was removed. ●

FOR MORE INFORMATION, *contact Dr. Sawaya at (713) 563-8749 or Dr. Weinberg at (713) 563-8705.*

Raloxifene Effective for Breast Cancer Prevention

Osteoporosis drug edges past tamoxifen in national STAR trial.

by Kathryn Carnes

A new option for breast cancer prevention may soon be available to physicians and their patients. In a huge multi-center study, raloxifene (Evista), a common osteoporosis drug, was shown to be as effective as tamoxifen (Nolvadex) in preventing invasive breast cancer but had fewer side effects.

The much-anticipated results were from an initial analysis of data from the Study of Tamoxifen and Raloxifene (STAR). STAR is a clinical trial designed to compare the two drugs' abilities to reduce the incidence of breast cancer in postmenopausal women at increased risk for developing the disease. This study, which accrued almost 20,000 women between July 1999 and November 2004, is a project of the National Surgical Adjuvant Breast and Bowel Project (NSABP). Major funding for the trial is provided by the National Cancer Institute (NCI).

Houston-based M. D. Anderson Cancer Center enrolled more than 400 STAR participants. Among the 195 participating clinical cancer centers, M. D. Anderson ranked second in overall accrual and third in the enrollment of minority women, after Puerto Rico and Hawaii.

Both raloxifene and tamoxifen were equivalent in reducing the incidence of invasive breast cancer in postmenopausal women at increased risk for the disease by about 50% compared with the expected incidence based on historical data (the STAR trial did not include a control arm).

But perhaps more exciting, researchers said, is that raloxifene (given at a dose of 60 mg once a day) achieved this level of efficacy while conferring a lower incidence of side effects than tamoxifen (given at a dose of 20 mg once a day).

> **"When you are talking about prevention, particularly when you are asking women to take a drug for 5 years of their lives, the side effect profile becomes very important."**
>
> **– Dr. Therese Bevers**

"When you are talking about prevention, particularly when you are asking women to take a drug for 5 years of their lives, the side effect profile becomes very important," said Therese Bevers, M.D. Dr. Bevers is the medical director of M. D. Anderson's Cancer Prevention Center and served as the institution's principal investigator for STAR.

Tamoxifen, a selective estrogen receptor modulator, made headlines in 1998 when the U. S. Food and Drug Administration (FDA) made it the first approved agent for the chemoprevention of breast cancer in women at increased risk. However, tamoxifen can cause rare but serious side effects. Specifically, it has been shown to increase the risk for endometrial and other uterine cancers, blood clots and strokes, and cataracts. Tamoxifen has also been shown to increase menopausal symptoms (e.g., hot flashes) and minor gynecologic problems (e.g., vaginal dryness).

The STAR results show that raloxifene, a second-generation selective estrogen receptor modulator, has fewer risks. Compared with women taking tamoxifen, those taking raloxifene had

- **36% fewer uterine cancers (including endometrial cancer),**
- **36% fewer pulmonary embolisms,**
- **26% fewer cases of deep-vein thrombosis, and**
- **21% fewer cataracts.**

"I think that the results are very exciting," Dr. Bevers said. "A lot of women and their doctors have not elected to pursue tamoxifen as a breast cancer risk reduction agent for a variety of reasons, including the small but real risk of developing serious side effects. Now we are talking about a drug, raloxifene, that they are very familiar with and have been using for many years as an osteoporosis preventive agent. What the STAR data are really providing them with is another benefit of raloxifene use."

The STAR trial was prompted by findings from an osteoporosis study evaluating postmenopausal women taking raloxifene to prevent osteoporosis. An incidental finding of the study indicated a lower-than-normal

incidence of invasive breast cancer in study participants. The STAR data confirm that the benefit is also conferred to postmenopausal women at increased risk for breast cancer, a group numbering about 9 million in the United States, Dr. Bevers noted. Raloxifene's maker, Eli Lilly & Co., has announced its intention to ask for FDA approval of raloxifene for the chemoprevention of breast cancer in postmenopausal women.

So far, the STAR data do not indicate that raloxifene and tamoxifen conferred different benefits related to race, age, family history, or other breast cancer risk factors; likewise, when breast cancers did occur, the treatment groups did not differ in terms of the size of the primary tumor, lymph node involvement, or estrogen receptor status. Even the costs of tamoxifen and raloxifene are similar, with the former averaging about $100/month and the latter about $75/month, the STAR researchers noted.

Although the STAR findings are compelling, tamoxifen will not soon be abandoned, Dr. Bevers noted. STAR enrolled only postmenopausal women; tamoxifen, conversely, has been approved for use in both pre- and postmenopausal women. In addition, raloxifene was not as effective as tamoxifen in controlling the incidence of noninvasive breast cancers (lobular carcinoma in situ and ductal carcinoma in situ). This finding is in concordance with previous research, but the reasons for it remain unclear.

The NSABP is eagerly anticipating the next study in the fight against breast cancer to open late fall 2006. Its plan to compare raloxifene and an aromatase inhibitor has already been submitted to the NCI for approval. Aromatase inhibitors have been shown to be more effective than tamoxifen in preventing second breast cancers. Plans for participation are underway at M. D. Anderson. Physicians interested in learning more about referring to or participating in breast cancer prevention clinical trials may contact (713) 792-8064.

More information about STAR is on M. D. Anderson's Web site at www.mdanderson.org/star, the NSABP Web site at www.nsabp.pitt.edu, and the NCI's Web site at www.cancer.gov. ●

IN BRIEF

Lung Cancer Susceptibility Runs in Families

Researchers at M. D. Anderson have documented a 25% increased risk of developing one of a number of cancers in first-degree relatives (parents, siblings, offspring) of lung cancer patients who have never smoked compared with families of people who neither smoke nor have lung cancer.

Researchers say their study, one of the largest ever done and the only one to include both men and women never smokers and to inquire about the smoking history of their relatives, strongly suggests that these lung cancer patients and their affected relatives share an inherited genetic susceptibility to cancer.

"This study demonstrates the importance of familial factors in the general development of cancer," said the study's first author, Olga Gorlova, Ph.D., an assistant professor in the Department of Epidemiology. "These susceptibility factors can be environmental but are more likely to be influenced by genetic factors, because genes control pathways common to a number of cancers."

Such marked cancer susceptibility also likely explains why patients in this study, who never smoked but might have been exposed to secondhand smoke, developed lung cancer in the first place, she said.

The research team, headed by Margaret Spitz, M.D., professor and chair of the Department of Epidemiology, looked at whether 2,465 first-degree relatives of 316 lung cancer patients who never smoked developed cancer. They also established a matched comparison group of 2,442 first-degree relatives of 318 "controls"—individuals who also never smoked but did not have lung cancer. They discovered the following:

- First-degree relatives of lung cancer patients had a 25% increased risk of developing any type of cancer.
- Relatives of these patients had a 68% higher risk of developing lung cancer.
- Relatives of patients were about 10 years younger than relatives in the control group when they were diagnosed with cancer.
- Family members of patients had a 44% excess risk of young-onset cancers—those diagnosed before age 50.
- There was more than a six-fold risk of developing young-onset lung cancer in these families.
- Mothers of patients had more than a two-fold risk of developing breast cancer.

"It has long been observed that cancer seems to aggregate in some families more than in others, and with the help of this unique group of lung cancer patients and their relatives, we can begin to understand why that might be the case," said Dr. Spitz.

Should Low-Risk Prostate Cancer Be Treated?

A new study will follow eligible low-risk prostate cancer patients with "watchful waiting" to determine if they can avoid or postpone therapy and related side effects but still live as long as patients who immediately receive invasive therapy.

Some men diagnosed with low-grade prostate cancer throughout the country will undergo active surveillance at M. D. Anderson for their disease, having changes monitored through regular prostate specific antigen (PSA) tests, biopsies, and check-ups.

The study will provide key information for the future development of clinical guidelines for watchful waiting and will also try to identify molecular markers that will better predict a person's risk of developing aggressive disease that requires treatment.

"With the advent of the PSA test, we now see prostate cancer detected much earlier. But because of the sensitivity of the test, clinically insignificant tumors sometimes are over-diagnosed and patients may, as a

(Continued on **page 6***)*

(*Continued from* **page 5**)

consequence, be over-treated with radiation and surgery," said Jeri Kim, M.D., principal investigator of the study and associate professor in the Department of Genitourinary Medical Oncology at M. D. Anderson. Researchers suspect that managing low-risk disease through surveillance may outweigh the risks and side effects of treatment. This study, and similar ones around the country, will seek to determine which patients are the best candidates for the watchful waiting approach.

"Prostate cancer is one of only a few cancers that can be latent in the body for some time and not require immediate treatment," said Dr. Kim. "Many researchers have documented over the years that many men die *with* their disease rather than from it. While we need to intervene early, we also need to intervene appropriately with respect to the stage of disease, the man's age, his health in general, and quality of life."

For more information on the watchful waiting study for men with early-stage prostate cancer, call (713) 563-1602.

Assessing Lung Cancer Risk

Physicians have little to help them predict the development of lung cancer in their patients—even a history of heavy smoking doesn't really help, since only a small fraction of lifetime smokers develops the cancer.

Now, however, researchers at M. D. Anderson Cancer Center are developing a risk assessment model that they hope will promote earlier detection of lung cancer in those smokers identified to be most at risk.

"Our goal is to develop an instrument that can help physicians estimate risk for developing lung cancer, like the Gail model does for breast cancer, or the Framingham model used to predict heart disease," said the study's first author, Matthew Schabath, Ph.D., a postdoctoral researcher in the Department of Epidemiology.

The analysis is based on research that compared the medical history and DNA repair capacity profiles of 2,134 lung cancer patients with the same data from 2,295 matched healthy individuals.

The prototype model is designed to first evaluate risk using only medical history and lifestyle factors, if that is all that is available, or a combination of medical history and genetic factors. For example, DNA repair capacity can increase or reduce a person's risk of developing cancer. To the model, researchers added data from a laboratory test that measures how efficiently subjects' lymphocytes drawn into a test tube repair damage from a carcinogen in tobacco smoke.

This model showed, for example, that:

- Heavy smokers who have been diagnosed with emphysema exhibit nearly a four times higher risk of lung cancer than light smokers without emphysema.
- This risk increases to nearly 11-fold if a person with the same history of emphysema and heavy smoking also has inefficient DNA repair capacity.

Clinical variables that appear to protect against lung cancer development are also being incorporated into the model, Dr. Schabath said. For example, they have estimated that:

- Individuals with a history of allergies (defined by a history of hay fever) have a 29% reduced risk of lung cancer.
- Such individuals who also exhibit efficient DNA repair capacity have a 56% reduced risk of developing lung cancer, compared with people who do not have allergies but have poor DNA repair capacity.

The model is a work in progress, said senior author Margaret Spitz, M.D., professor and chair of the Department of Epidemiology. The next steps in building the model are to add to it variations in important genetic pathways that control cellular functions and additional environmental and dietary factors.

"Early detection is key to successful treatment of any cancer, and this model is designed to help physicians identify and screen those smokers at highest risk for lung cancer," Dr. Spitz added.

Promising Option for Herceptin Resistance

Breast cancer patients with HER2-positive tumors that don't respond to Herceptin (trastuzumab) may benefit from a cocktail therapy that includes Herceptin along with one or more PI3K-inhibiting agents, say researchers at M. D. Anderson Cancer Center.

Their findings were made in cell culture and mouse studies but are so promising that a phase I/II clinical trial will start at M. D. Anderson in HER2-positive breast cancer patients whose disease has progressed despite Herceptin treatment.

"More than half of patients with HER2-positive tumors don't respond to Herceptin as a single agent, and our research found that the presence of the protein PTEN is a powerful predictor of response," said the study's lead author, Dihua Yu, M.D., Ph.D., a professor in the Department of Surgical Oncology.

PTEN is known to block the effect of a growth-promoting protein known as PI3K, which itself controls an oncogenic pathway. Dr. Yu decided to test what would happen if she administered an experimental drug that blocks PI3K and thus mimics PTEN's tumor suppressor activity.

In this study, the research group tested seven different PI3K inhibitors that are either used or under development for clinical trials. They found that one, RAD001 (everolimus), had better antitumor activity when combined with Herceptin than did Herceptin or RAD001 alone.

Another PI3K inhibitor, TCN-P (triciribine), showed significant benefit when used in combination with Herceptin, Dr. Yu said.

"If this drug cocktail shows benefit in clinical trials, we hope to identify patients who won't respond to Herceptin before they start the treatment and offer them a new and beneficial drug combination," Dr. Yu said. "Patients who don't respond to Herceptin tend to have poor outcomes, so we hope this strategy will help them."

HOUSE•CALL

The Many Benefits of Massage

Long touted as a way to ease muscle strain and foster relaxation, massage is now being used to relieve some of the side effects of cancer and cancer treatment. As a complementary therapy, massage assists circulation, restores energy, and enhances emotional well-being.

Massage has been shown to reduce the fatigue, pain, anxiety, and nausea that cancer patients often experience, according to Ki Y. Shin, M.D., a rehabilitation physician and an associate professor in M. D. Anderson Cancer Center's Department of Palliative Care and Rehabilitation Medicine. Although not a treatment for cancer, massage seems to ease symptoms of the disease and to help patients cope with the side effects of treatment. It improves their satisfaction with hospital stays and can also improve quality of life, said Dr. Shin.

Types of massage

Massage has been around for centuries. Originating in traditional Chinese medicine, it was also once used to treat illness in Japan and India and in ancient Egypt, Greece, and Rome. It can be done while the recipient is seated in a chair, lying on a table, or in a hospital bed.

Massage is a touch therapy in which a client's muscle groups are stroked, kneaded, or stretched. Among the various forms of massage is Swedish massage, which is very popular in the U.S. and which uses kneading actions to enhance circulation or long, gentle strokes to communicate calmness to the skin. Deep tissue massage focuses on the deeper underlying areas of muscle. Another type of massage is manual lymphatic drainage, which uses very light pressure in gentle rhythmic motions to increase the flow of lymph fluid out of swollen tissues. The National Cancer Institute says that this form of massage is an effective therapy for lymphedema, the retention of proteins and water in the tissues that is sometimes a side effect of cancer treatment. Because of potential side effects and injury, manual lymphatic drainage massage techniques should only be performed by a health practitioner with lymphedema-specific training and certification.

Massage has been shown to reduce the fatigue, pain, anxiety, and nausea that cancer patients often experience.

Who should not receive massage

Patients with certain medical conditions, however, could be harmed by receiving a massage. Those who should not get massage therapy, Dr. Shin said, include patients with blood clots or a tumor or active disease in the area to be massaged. Patients taking blood-thinning or anticoagulant medications or those who have an unstable spine or other fractures, low platelet counts, and certain blood disorders should not receive deep tissue massage. A variety of other medical conditions such as skin fragility after radiation treatment or chemotherapy, infections, bone metastasis, or excess fluids outside of the lungs may require adjustments in massage therapy. A patient should not be massaged in the region of a tumor or enlarged lymph node, as there may be a risk of dispersing the cancerous cells.

The massage therapist

It is important for a person with cancer to pick a massage therapist who has training in the special needs of cancer patients, Dr. Shin said. Such a therapist will screen each person to see if a massage is appropriate and, if necessary, modify the massage to accommodate the client's medical condition. This might mean, for instance, reducing the pressure of the massage therapist's touch in order not to irritate a client's swollen tissues or avoiding certain areas near a tumor or surgical incision. It is vital for a massage therapist to consult with a patient's oncologist before treatment, and it is also important for physicians to know when a patient is undergoing this complementary therapy.

For more information

To find a qualified massage therapist with experience working with cancer patients, contact the American Massage Therapy Association by calling 1-877-905-2700, or visit their Web site at www.amtamassage.org. For information on studies on massage and cancer patients, visit www.mdanderson.org/cimer and then click on Reviews of Therapies and Manipulative & Body-Based Methods. ●

For more information, talk to your physician, or:

- *call the M. D. Anderson Cancer Center Information Line at (800) 392-1611 (Option 3) within the United States.*
- *visit www.mdanderson.org.*

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DiaLog

Cancer Vaccines and Immunotherapy

Patrick Hwu, M.D.
Professor and Chair
Melanoma Medical Oncology

Over the past century, perhaps the medical advance with the greatest impact on global health has been the development of vaccines to prevent infectious diseases. Many cancer researchers are now working to harness the power of the immune system against cancer.

The immune system consists of a diverse group of cells that work together in coordinating an attack on invading pathogens. Dendritic cells are the sentinels that first detect the invading pathogens and subsequently stimulate the lymphocytes, which can eliminate the invaders. Lymphocytes are capable of recognizing small molecular differences in antigens. Therefore, cancer vaccines, which aim to stimulate the immune response against cancer, may be an ideal means to molecularly target tumors.

However, it is significantly more challenging to develop vaccines against cancer than against bacteria and viruses because tumors are not foreign invaders. Despite these challenges, we are making significant progress. We are applying principles learned from the natural immune response against pathogens to the generation of an antitumor immune response.

Although vaccines against infectious diseases have been highly successful, they can only prevent disease and are not able to treat active infections. This is because it can take several weeks to mount an optimal immune response. Therefore, it may be unrealistic to think that we will be able to treat active metastatic cancer with a vaccine alone. Perhaps ultimately the best use of cancer vaccines will be to prevent cancer recurrence once the initial disease has been eliminated with surgery or chemotherapy. This situation applies to a large proportion of patients who present with cancer.

For patients with more advanced disease, we have had some success with adoptive T-cell therapy, which is the infusion of large numbers of tumor-reactive lymphocytes. In people with some cancers, there are lymphocytes that are capable of recognizing the tumor. However, they are obviously not functional since the cancers in these patients continue to grow. After removing the tumor, we have grown large numbers of the infiltrating lymphocytes in the laboratory. Reinfusion of these lymphocytes in patients with advanced melanoma has significantly reduced tumor volume in half of the patients. We are currently trying to improve these results by combining adoptive T-cell therapy with cancer vaccines.

This is an exciting time in cancer research with our increased understanding of the molecular nature of cancer and the immune response. Ultimately, our success will likely depend on the rational combination of appropriate chemotherapies, targeted therapies, immunotherapy, and the rapid translation of laboratory advances to the clinic. ●