



REPORT TO PHYSICIANS

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Oncology

Modern cancer therapy owes much to advanced diagnostic imaging, which can reveal a tumor's precise location, size, and response to therapy. Next step: seeing cancer processes at the molecular level.



Dr. Homer Macapinlac says
*PET/CT imaging has benefited the
entire spectrum of cancer care.*

Worth More than a Thousand Words

By Sunni Hosemann

At one time, oncologists were taught to gauge the size of palpable tumors by practicing with wooden balls under a sheet and using calipers to measure them. This training was intended to help answer a very important question when monitoring cancer in the clinic: had the tumor changed?

Of course, wooden balls and calipers have long since given way to modern diagnostic imaging, which allows oncologists not only to “see” neoplasms and calculate their volume but also to determine whether a tumor is metabolically active. The latter is important because in some kinds of cancer, such as lymphoma, the tissue mass that may remain after treatment can look the same as it did before but, in fact, no longer be an active cancer.

One of the most important recent advances in imaging has
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Worth More than a Thousand Words

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been the fusion of positron emission tomography (PET) and computed tomography (CT) scanning. Fusing the images provides more sophisticated information than simply doing the scans separately and comparing the results. CT scans yield sharp anatomic images but don't show physiologic activity; PET scans have relatively lower spatial resolution but do show metabolic activity. Over the past few years, fused PET/CT scans have proven invaluable in helping oncologists make more accurate diagnosis and staging assessments, choose the most appropriate therapies, and determine whether a therapy is effective against a cancer.

Experts at The University of Texas M. D. Anderson Cancer Center are working far beyond that, however.

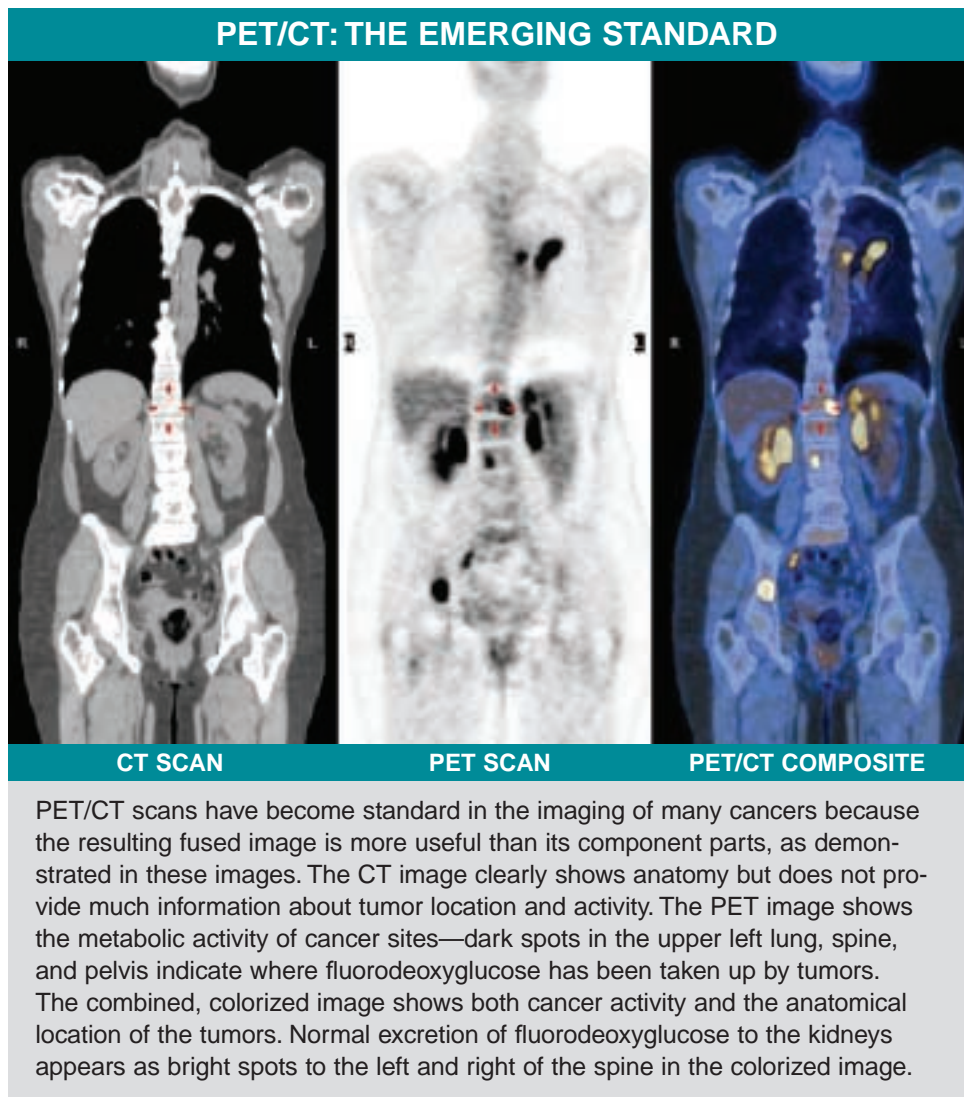
"We want images to show what is happening not just at the cellular level, but much deeper," said Donald Podoloff, M.D., a professor of nuclear medicine and head of M. D. Anderson's Division of Diagnostic Imaging. "We want to see whether the signal pathways within cells have shut off after a course of chemotherapy. We want to see whether receptor sites on cell surfaces are open or blocked.

"We want to see *molecules*."

PET/CT: How it works

Both PET and CT have been staples of imaging in oncology for years, but the fusion of the two yields more information than do the two separately. During a PET/CT procedure, the same machine does both scans and shows each separately plus a third set of co-registered (or fused) images. The yield is an image showing an anatomically localized area (CT) of metabolic activity (PET).

The metabolic imaging component of the technology is actually based on a long-understood concept in cancer biology. Scientists have known since the 1930s that cancer cells are metabolically more active than normal cells: they grow, divide, and consume sugars more aggressively. So, the current generation of PET scans uses fluorodeoxyglucose, which is 2-deoxy-D-glucose labeled with fluorine-18, a positron emitter.



The resulting substance "goes where glucose goes, which is into metabolically active cells," said Homer Macapinlac, M.D., professor in and chair of M. D. Anderson's Department of Nuclear Medicine. Once cancer cells take up the substance, he explains, the trapped fluorodeoxyglucose gives off gamma rays that the PET camera can "see"—and the information is translated on the screen into an accurate image of the tumor's glucose uptake.

There are practical advantages of PET/CT as well. "Our PET/CT scans are faster than conventional PET scans because the CT is used for attenuation correction of the image, which takes seconds, while traditional correction methods took as long as the PET scan itself—about 20 minutes," said Dr.

Macapinlac. "Also, the total radiation exposure to the patient is less than that of standard diagnostic CT scans, so PET/CT scans can be safely performed on infants and the elderly."

Benefits of PET/CT

The benefits of PET/CT images in the entire spectrum of cancer care—from diagnosis and treatment planning to evaluation of treatment response—have come into focus in recent years as the technology has become a standard practice at M. D. Anderson. "This is a great help to patients," said Dr. Macapinlac. "They want to know if they have cancer, and if they do, they want to know how bad it is. They also want to know if, when we give a treatment, it's working. PET/CT can tell us

that better and faster than X-ray or CT or PET alone.”

Diagnosis

PET/CT has proven particularly valuable in diagnostic applications for cancers that are not easily reached for biopsy, such as lung cancer. An experienced evaluator can easily distinguish between a benign lung mass and a malignancy. For tumor masses that are not homogeneous—where biopsy results might differ depending on the location within the tumor that was sampled—PET/CT can pinpoint areas of increased activity within a tumor that should be targeted for biopsy, as they will be the most aggressive parts of the tumor. And in the best cases, “We get to tell patients they don’t even have cancer,” said Dr. Macapinlac.

Dr. Macapinlac likes a challenge, and if he could be said to have a favorite kind of case, it would be cancer of unknown primary site. These cases involve patients who present with metastatic lesions whose origin is a mystery. Sometimes an oncologic pathologist can provide clues, but sometimes the primary tumor is never found. “Using PET/CT, we’ve been able to find 10% to 15% of them,” he said. It may not sound like a lot, but for those patients, finding the primary site can mean the difference between receiving successful, targeted treatment or a potentially less successful, best-guess regimen. In one recent case, a young patient presented with a cancer-involved lymph node in his neck. The primary tumor was found buried in the mucosa under his tongue, invisible to other imaging modalities.

Staging

Cancer staging is a major determinant of treatment choice, and lymph node status is an important aspect of staging for most cancers. Cancer-involved lymph nodes are not necessarily enlarged, so a patient staged with conventional modalities might appear to have only localized disease when, in fact, it has spread to the lymph nodes. PET/CT can be used to determine whether any nodes are involved. It can

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– Dr. Homer Macapinlac

also be used to find distant metastatic disease that used to be considered occult—that is, no symptoms or clinical signs, no abnormal results in key laboratory studies (such as alkaline phosphatase testing), and no masses visible by conventional imaging. Because the discovery of involved lymph nodes or distant metastases changes the disease stage and therefore treatment, PET/CT studies are becoming an integral tool in the staging of many cancers at M. D. Anderson.

Response to treatment

“Sometimes after chemotherapy,” said Dr. Macapinlac, “a tissue mass will continue to look the same for months with conventional images.” This can leave the clinician uncertain that the

treatment worked; for the patient, such uncertainty can be anguishing.

Lymphomas represent a case in point: it can be difficult to differentiate the tumor tissue from normal tissue with conventional imaging or, in the case of disseminated disease, even with multiple biopsies. PET/CT can help guide further therapy by either confirming response or signaling the need for a change. This information can also be prognostic: lymphoma patients with a negative scan after two or three cycles of chemotherapy have better rates of progression-free and overall survival. “So we’re able to tell them right away that it’s working and that they will likely be disease-free for a long time,” said Dr. Macapinlac. For patients who are undergoing aggressive and often expensive courses of treatment, such as high-dose chemotherapy and bone marrow transplants, the images provided by PET/CT are considered so valuable that the scans have become part of the lymphoma practice guidelines at M. D. Anderson. Although PET/CT is expensive, it has been shown to reduce costs in the long run and so is eligible for coverage by Medicare and most insurance plans.

The next generation

The experience with PET/CT using fluorodeoxyglucose provides a paradigm for the future in which radiopharmaceutical agents will be used in combination with imaging modalities to look ever deeper into the body. Needed next: novel tracer substances that can show processes other than glucose metabolism and even more sophisticated imaging instrumentation to yield further insight into the behavior, growth, and treatment of tumors.

Enter Juri Gelovani, M.D., Ph.D., professor in and chair of M. D.

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“We want images to show what is happening not just at the cellular level, but much deeper,” says **Dr. Donald Podoloff**. “We want to see molecules.”

Worth More than a Thousand Words

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Anderson's Department of Experimental Diagnostic Imaging. A pioneer in molecular imaging, Dr. Gelovani has been tapped to head M. D. Anderson's Center for Advanced Biomedical Imaging Research, a research collaborative that will bring together the many specialties necessary to advance these technologies and move them from research labs to clinical use.

"Some therapies have been difficult to translate to the clinic, in part because they are so difficult to evaluate," said Dr. Gelovani. Gene therapy is an example. The location, magnitude, and duration of gene expression cannot be assessed by biopsy alone, and evaluation of therapeutic gene expression in the whole body would require biopsies of multiple sites—an unfavorable option. Even for therapies whose effects can be assessed by biopsy, the procedure's invasive nature makes it impractical to do frequently. Next-generation imaging procedures being developed in the Center for Advanced Biomedical Imaging Research will show therapeutic processes as they take place.

Tracers

One of the key elements of this research will be the development of radiopharmaceuticals (or tracers) that, combined with advanced imaging modalities, show processes within cells



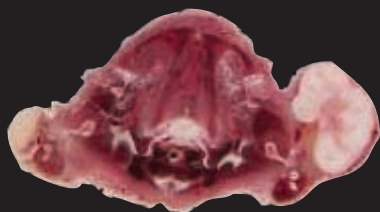
Dr. Juri Gelovani is among the M. D. Anderson researchers developing novel imaging agents that can help predict responsiveness to therapy or "report" whether a particular therapy was effective.

that conventional and newer molecular therapies are meant to target. For example, if a drug's mechanism is to disrupt a specific cell-signaling pathway, such a tracer would show whether, in fact, the pathway was disrupted or the receptor was adequately inhibited.

Molecular tracing compounds can be designed to detect the presence or absence of specific cell-surface receptors or to determine whether certain cell

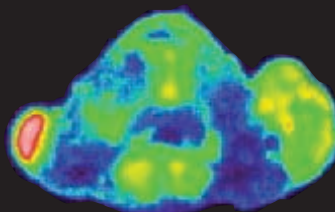
signals are turned on or off, and such tracers can be employed before and after particular therapies. For example, tracers that home in on growth factors or on cell-surface receptors specific to new blood vessels can monitor the success of anti-angiogenesis agents non-invasively and can reveal vessels beginning to sprout in a tumor while the tumor is still too small to image conventionally.

CUSTOMIZING THERAPY WITH RECEPTOR-SITE IMAGING



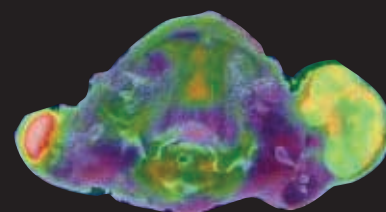
HISTOLOGY

A radiolabeled tracer being developed by Dr. Gelovani and colleagues can image active-mutant EGFR, the presence of which predicts responsiveness to EGFR-inhibitor therapy. The images above show human lung cancers growing in a



AUTORADIOGRAPHY

mouse—one tumor on the left side of the specimen and the other on the right. In the autoradiography and autoradiography/histology images, the EGFR is indicated by reds and pinks. The tumor on the left of the specimen demonstrates homoge-



AUTORADIOGRAPHY/HISTOLOGY

neous EGFR expression, while the tumor on the right is heterogeneous. Images such as these in humans could help individualize therapy without the need for biopsy—particularly beneficial in patients with heterogeneous or multiple tumors.

Reporter genes

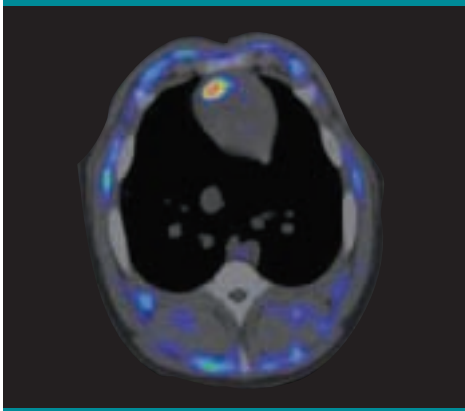
Another class of agents—reporter genes—can be attached to therapeutic agents, including gene therapy. “These substances do not perturb the process,” said Dr. Gelovani. “They simply trace it.” The role of reporter genes is to take up radioactive substances so they can be imaged—where they are active, so is the therapy. Dr. Gelovani invented the process for imaging the PET reporter gene HSVTK (herpes simplex viral thymidine kinase), and today, he and colleagues are working on adding it to an immunotherapy for leukemia in which T cells are given to initiate a graft-versus-leukemia response. When the T cells are genetically modified with HSVTK, clinicians will be able to observe the graft-versus-leukemia response with PET/CT and quickly detect and treat any undesirable graft-versus-host response before clinical symptoms develop.

Stem cells labeled with PET reporter genes and those cells’ progeny can continue to report for months or years, enabling researchers to know where they go, whether they multiply, if and how they differentiate, and when they die. Dr. Gelovani refers to this as “theragnostics” or “imageable therapy.” He is developing one such application to repair cardiovascular damage with colleagues in the Department of Veterinary Medicine and Surgery, the Department of Stem Cell Transplantation and Cellular Therapy, and Texas Heart Institute.

Repairing tissue damage

The team is targeting tissue that has been damaged by an infarct or chemotherapy—as Dr. Gelovani points out, the development of regenerative therapy for cardiovascular damage is increasingly important as cancer survivors live longer. The experimental therapy, which is moving toward trials in humans, is done with a minimally invasive procedure: a catheter is inserted into a major vessel and threaded to the heart. From inside the organ, a portal needle injects gene-labeled stem cells directly into the myocardium. PET/CT can then be used to visualize where and how well the cells have grafted to

USING GENES TO TRACK SUCCESS



PET/CT SCAN OF GENE-LABELED STEM CELLS

In this fused PET/CT image of a pig heart, the area of reds and yellows shows where stem cells have been injected to repair cardiovascular damage. The cells are labeled with reporter genes, which can be imaged by PET. Such images indicate where the stem cells have grown into heart tissue, and, since they are labeled genetically, it should be possible to track the cells’ progeny for years. Dr. Gelovani refers to this type of technology as “theragnostics” or “imageable therapy.”

the original tissue; repeated imaging indicates the viability of the stem cell-derived tissue and its contribution to the heart’s contractile function.

“Because the stem cells are labeled genetically, it should be possible to monitor the fate of the stem cell-derived tissue over the course of several years or as long as the tissue persists,” said Dr. Gelovani. Imaging is crucial to assessing the therapy because the heart cannot tolerate repeated biopsies.

Predicting therapy response

Another new imaging technology that will soon be moving into human trials can detect whether a tumor will respond to therapy with epidermal growth factor receptor (EGFR) inhibitors—before the therapy is given. This technology uses a receptor-site imaging agent that can show through PET/CT the presence of overex-

pressed EGFR, which is thought to cause many lung and brain cancers. “The presence of such receptors has been associated with a dramatic response to therapy with specific EGFR inhibitors, such as erlotinib,” said Dr. Gelovani, who is developing the imaging agent with Roy Herbst, M.D., professor and section chief of Thoracic Medical Oncology, and Waun Ki Hong, M.D., professor and head of the Division of Cancer Medicine.

However, EGFR is present in only a small segment of the patient population—about 8–10% of lung cancer patients, for example. Thus, using imaging to identify those patients who would benefit from EGFR-inhibitor therapy would allow for greater customization of effective therapy, without the need for biopsy. The imaging agent also can show which parts of a heterogeneous tumor have activated EGFR, which would provide a treatment path when multiple tumors—some that may over-express EGFR and others that may not—are present.

Better outcomes ahead

This arsenal of new and upcoming imaging therapies has taken plenty of imagination to develop, but it takes little imagination to see the potential. As has happened with PET/CT, technologies such as tracer compounds and reporter genes promise earlier and more accurate diagnoses, more targeted treatments, and, ultimately, better outcomes.

“This work points to a day when patients could have a cancer or tissue damage imaged and treated—non-invasively—within a matter of hours or days, and we would be able to evaluate the effectiveness of the therapy just as quickly,” said Dr. Macapinlac. “We need to prove this happens at the tissue level so that molecular imaging becomes a surrogate marker for these processes. This is the future of diagnostic imaging.” ●

For more information, contact Dr. Macapinlac at 713-792-7126 or Dr. Gelovani at 713-563-4875, or visit www.mdanderson.org/departments/physrelations.

A Step Forward for Stents

Improved design is reducing complications from pancreatic cancer.

By Dianne Witter

Jeffrey H. Lee, M.D., guides the endoscope and its attached accessories carefully into the patient's esophagus, keeping track of the scope's whereabouts on monitors that show real-time video images. Introduced through the endoscope is a stent made of thin, flexible metal mesh.

The stent, collapsed for the journey, is roughly the diameter of a straw. Dr. Lee, an associate professor in M. D. Anderson's Department of Gastroenterology, Hepatology, and Nutrition, guides the device through the duodenum to the opening of the bile duct, which is his destination.

With the help of images from computed tomography, endoscopic ultrasonography, and fluoroscopy, he carefully threads a guide wire into the obstructed passageway and advances the stent into the bile duct. Once the stent is placed, it expands to open the duct and allow bile to flow again. On the monitor, a gush of dark bile from the end of the stent signals success.

An obstructed bile duct is a frequent complication of pancreatic cancer that can cause fever and potentially life-threatening infection. As tumors in the head of the pancreas grow, they tend to crowd the bile duct, narrowing the passageway until the flow of bile is slowed or even stopped. Plastic stents have been used for years to relieve such obstructions, but these stents have significant drawbacks, such as the tendency to clog within 3 months of placement. Once a stent is occluded, complications such as cholangitis and cholestasis are likely to develop, and a new stent must be placed.

Fortunately, stents—and the materials that go into them—are improving



Dr. Lee (left) implants a new-generation metal stent to relieve a bile duct obstruction.

quickly. Their use has become more important as therapy changes.

"More and more, physicians are administering preoperative chemoradiation in locally advanced pancreatic cancer, which increases the time to surgery and, therefore, increases the possibility of a biliary obstruction," said Dr. Lee. "That has elevated the urgency of the need for stents that will stay open throughout preoperative treatment."

The current state-of-the-art material for stents is a nickel-titanium alloy. A wire-mesh stent made of this alloy is pliable, conforms to the shape of the structure it is in, can be compressed for transport during placement, and is very unlikely to migrate once in place.

"In a 2005 study, we found that the metal stents didn't get occluded as quickly as plastic stents and were associated with a lower incidence of cholangitis. Also, there was a reduced need for repeat endoscopic retrograde cholangiopancreatography (ERCP) with metal stents, and there were no more surgical complications than with plastic stents," said Dr. Lee. "We also discovered that the metal stents, when appropriately placed, didn't interfere with subsequent tumor resection.

"Based on these findings, at M. D. Anderson we changed from plastic to metal stents to treat biliary obstruction resulting from pancreatic cancer, and

now others in the medical community are following suit."

There are more advances on the horizon. M. D. Anderson researchers led by William Ross, M.D., associate professor in the Department of Gastroenterology, Hepatology, and Nutrition, are taking part in a multi-institution, phase III trial of a new metal stent that is covered with silicone to prevent tumor growth into the stent. Covered metal stents are expected to reduce the need for additional ERCP procedures and to lengthen the patency period. Concerns about covered metal stents, as opposed to metal mesh-weave stents, include the possibilities of stent migration and obstruction of the cystic duct.

Also in the pipeline are bioabsorbable stents designed to be taken up by the body within 1 to 3 months after placement. These have shown significant promise in animal studies and will likely move to human trials soon, especially for benign causes of biliary obstruction.

Developing more advanced stents may not deliver a cure, said Dr. Lee, but it will improve patients' quality of life and help provide safer passage from diagnosis to surgery. ●

For more information, contact Dr. Lee at 713-794-5073.



Getting the Most From Your Doctor Visit

For many people, a visit to the doctor's office can be stressful and even a little scary. But by taking an active role in your health care, you can help make sure that your next doctor visit is a success.



Be ready

Your symptoms, lifestyle, and history will play an important role in your diagnosis. So, before you even set foot inside the waiting room, gather enough information to give your doctor a full picture of your situation. Don't rely on memory alone. Instead, make written lists:

- List any current or previous medical conditions you have had and any treatments or surgeries you have undergone, including dates. It helps to have copies of your medical records from other physicians on hand as well, especially if you are a new patient.
- Make a list of the medications you currently take, including prescription and over-the-counter drugs, herbal supplements, vitamins, and minerals. Note each medication's dosage, how often you take it, for how long you have taken it, and most important, why you take it. If you are unsure, bring the medication bottles with you.
- Write down any symptoms you are having. Describe how often you have them, when they first appeared, and how strong they are. Think of the usual questions your doctor might ask, such as "What brought you in today?" and "What kind of pain are you experiencing?" Keeping a daily journal of your symptoms can serve as a helpful reminder of exactly what you have experienced.
- Write down any questions or concerns you want to discuss with your doctor. If you have a lot of questions, focus on the two or three that are most important to you, discuss these in detail with your doctor, and schedule additional appointments to talk about the others.
- If possible, find out in advance how

much time you will have with your doctor. Knowing your time limit can help you stay focused as you plan for the appointment.

Be heard

Communicating with your doctor is the key to a successful visit. You and your doctor should agree on exactly what will be done during each step of your care, so make it a point to actively listen and to let your doctor know what you think.

- Speak up if you have questions or concerns, and if you don't understand something, ask again until you do. Your health is too important to worry about being embarrassed if you don't understand something your doctor tells you.
- Take notes to help you remember what you talked about during your visit. Jotting down information about treatment options or medications will help you understand and manage your condition. If your doctor refers you to a specialist, ask for several specific questions to ask the specialist, and write these down as well.
- If your doctor prescribes a new medicine, ask what the medicine is supposed to achieve.
- Ask your doctor for more information about your condition. Ask him or her to recommend Web sites, articles, and other sources where you can learn more. The more you know about your diagnosis, the better you can manage it.
- It may help to have a trusted family member or friend by your side during your doctor visit, especially if you're feeling overwhelmed or

stressed. This person can ask questions that you may not think of while you are under stress. He or she can speak up for you if you cannot do so yourself and later can help you remember the answers to questions you asked.

Be sure to follow up

Your care doesn't end when the appointment is over.

- Before leaving, find out the best way to contact your doctor in case you have questions about your care or any prescriptions.
- After the visit, educate yourself about your diagnosis, any medical tests you are undergoing, and your treatment plan. Review your notes and any information the doctor gave you along with any other sources he or she suggested.
- Talk with people you trust who have experienced the same treatments or procedures that you will undergo. They can help you prepare for the days and weeks ahead and can tell you what to expect and what worked best for them as they recovered.
- Finally, don't be afraid to seek a second opinion. If you are unsure about the nature of your illness and the best treatment, consult one or two other specialists. The more information you have about the options available to you, the more confident you will be in the decisions made. ●

Source: *Speak Up for Healthcare Safety*, The Joint Commission

For more information, talk to your physician, or:

- call askMDAnderson at 1-877-632-6789
- visit www.mdanderson.org.

OncoLog, December 2007
J. Munch

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DiaLog Is MRI Better for Breast Screening?

By **Huong Le-Petross, M.D.**

Mammography has been the only imaging modality used for breast cancer screening for the past 30 years and has resulted in at least a 30% reduction in the breast cancer-related mortality rate in women. However, in the women at high risk of breast cancer, annual screening mammography has low sensitivity. In young women at high risk, the greater density of their breast tissue may make it difficult to detect cancer early. Also, in women with inherited risks, such as carriers of *BRCA* mutations, tumors tend to grow faster than in non-carriers.

Most women at risk for hereditary breast cancer opt for intensive breast screening rather than bilateral mastectomies. For these women, there is a definite need for additional imaging modalities to detect cancer earlier. In six prospective studies, the addition of annual contrast-enhanced magnetic resonance imaging (CE-MRI) to mammography was compared to clinical breast examination, mammography, and/or ultrasonography. The studies indicated that CE-MRI in combination with mammography offers the best screening option for women at high risk.

The revised American Cancer Society guidelines for breast screening published in May of this year recommend MRI with mammography in patients who have a lifetime breast cancer risk of 20–25%. This includes women who have an inherited risk for breast cancer and first-degree rela-

tives of a *BRCA* mutation carrier.

However, the most appropriate screening intervals for these high-risk women are not clear because of a lack of good data.

At M. D. Anderson, high-risk patients are screened every 6 months, alternating between mammography and CE-MRI.

However, CE-MRI is not recommended as a screening tool for women with low to average breast cancer risk. This is partly due to technical limitations—a high false-positive rate is associated with MRI, and this rate may be even higher in the general population than in the high-risk population. (This recommendation may change as the technology matures.) Other drawbacks include the cost of an MRI exam and the added cost of follow-up studies.

It's also important to remember that, while CE-MRI is a beneficial adjunct to mammography and clinical breast exam in high-risk women, CE-MRI should not replace screening mammography. To date, no hard data are available to show whether breast MRI used as an adjunct to mammography affects the breast cancer-related mortality rate in the high-risk population. The limitations of MRI should be communicated to each patient and a screening plan individually tailored. ●



Dr. Le-Petross is an assistant professor in M. D. Anderson's Department of Diagnostic Radiology.

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