Completing the Job: Multidisciplinary Effort Restores Form and Function, Improves Patients’ Quality of Life

by Beth Notzon

Successful cancer treatment once meant simply that the disease had been eradicated and the patient survived—no matter how disfigured or disabled they may have become. More and more, however, cancer therapies are taking into account the preservation and reconstruction of function and appearance.

Geoffrey Robb, M.D., who chairs the Department of Plastic Surgery at The University of Texas M.D. Anderson Cancer Center, observed that when disfigurement and defects threaten a patient’s quality of life, “We may have treated that person for their cancer, but we didn’t complete the job. We want to see to it that a patient doesn’t stand out in line at the grocery store—that they don’t frighten people, don’t frighten their grandchildren.” Dr. Robb summed up the mission of plastic surgeons at M. D. Anderson in plain terms: “It is to restore the patient’s facial contour, breast contour, or extremity contour and (Continued on next page)

Dr. James Lemon, a professor in the Department of Head and Neck Surgery, holds a prosthetic ear designed to replace the one that the patient lost to cancer.
Restoring Form and Function
(Continued from page 1)

preserve and restore as much function as possible and in the end to restore their quality of life.”

Despite the important work they now do at M. D. Anderson, plastic surgeons are relative newcomers to the care of patients with cancer. Dr. Robb noted that before 1987, no full-time plastic surgeons were on staff at M. D. Anderson, only part-time surgeons who were called upon as needed. Now the Department of Plastic Surgery boasts 10 surgeons, making it one of the largest plastic surgery departments in the world. In fact, according to Dr. Robb, plastic surgery has become an important surgical adjunct for many of the patients who require surgical treatment for cancer at M. D. Anderson.

This transformation has been fueled primarily by the increasing complexity and extensiveness of cancer treatments. Called multimodality therapy, this new approach involves treating patients with a combination of chemotherapy, radiation therapy, and ablative surgery. Although it is very effective and can cure, such treatment can cause significant side effects. For example, in some cases, wound healing is compromised, and plastic surgeons may be called in to construct special flaps to cover the wound and promote healing. In women with breast cancer who are treated with radiation therapy and chemotherapy after mastectomy, the radiation therapy can cause temporary but severe dermatitis and the chemotherapy can further compromise healing, thus preventing breast reconstruction at the time of mastectomy. Plastic surgeons can help a woman at this time by simply explaining the process to her. As Dr. Robb said, “For that patient to remain calm and confident in her outcome, she has to have all of the possible problems explained to her well ahead of time, so that she can get through the deformity and the skin changes and be confident she will have restoration of her breast.”

The skills and expertise of plastic surgeons have made possible extensive ablative surgical procedures. In particular, new strategies have given patients with head and neck cancer a hope they did not have a few short years ago. Both the cancer and its treatment can leave these patients extremely disfigured. In many cases, facial paralysis can result from brain tumors, facial tumors, or tumors that involve the facial nerve. “It affects eyelid closure, cheek movement, the nose, the entire movement of the mouth on one side. It even involves the inside of the mouth and the ability of the inner structures of the mouth to support chewing, swallowing, and speech,” Dr. Robb explained. “We see a lot of patients with facial paralysis because we have many ways to treat it now.”

A particularly demanding challenge is patients with tumors that necessitate the removal of a large portion of the face. According to Rhonda Jacob, D.D.S., a professor in the Department of Head and Neck Surgery, facial prostheses can range from a tooth to an ear or nose or to a large part of the face. Dr. Jacob explained that dentists get involved in making facial prostheses because “the laboratory processes and materials that are used to make the facial prostheses are very similar to what goes on in a dentist’s office when we’re making teeth.”

Facial prosthetics brings together a team of plastic surgeons, prostodontists, and anaplastologists, who are usually artists or medical illustrators by training. At M. D. Anderson, James Lemon, D.D.S., a professor in the Department of Head and Neck Surgery, is the primary prostodontist involved in the construction of facial prostheses. Although the process is deceptively simple, it can take upwards of 1 to 2 weeks for a prostodontist and anaplastologist working full-time with a patient to come up with the final product. After a succession of various types of molds are made, a final silicone mold is created from which a very lifelike representation of the missing portion of the patient’s face is fashioned, using the same dyes and materials artists use. Dr. Robb explained that plastic surgeons assist the prostodontists in implanting magnets to help secure the prostheses in place and in creating the foundations for the prostheses.

Dr. Jacob emphasized, however, that a facial prosthesis is not just a mask. The prosthesis is constructed internally so that it restores function—the ability to speak, swallow, and chew. Needless to say, the results are great. The results are also very convincing. Dr. Jacob described one man who deemed his prosthesis a success because he kept bumping into people—his artificial eye looked so natural that people did not know that
he could not see out of it, and they no longer gave him a wide berth.

Microvascular surgery, another important advance in the practice of plastic surgery, debuted more than 25 years ago. By providing a blood supply to tissue grafts, it gave plastic surgeons the tool they needed to perform successful reconstructive surgical procedures. Dr. Robb explained that because of advances made in the intervening years, microvascular surgery is now successful 98% to 99% of the time. As a testament to the particular skills of the plastic surgeons at M. D. Anderson, the Department of Plastic Surgery conducts the largest microvascular surgery training program in the nation, currently training five to six microvascular surgeons a year.

One bright hope for the future of plastic surgery is tissue engineering, using cells from a patient’s own tissues for tissue and organ regeneration. Indeed, tissue engineering represents a brave new world for many specialties, not just oncology, that have struggled for years with less-than-satisfactory methods of replacing tissues. According to Charles W. Patrick, Jr., Ph.D., an associate professor in the Department of Plastic Surgery and director of the Laboratory of Reparative Biology and Bioengineering, tissue engineering has two main advantages over other methods of tissue replacement. “First, it is based on the patient’s own cells, so we don’t have to rely on foreign materials, and second, because we are using a patient’s own cells and we don’t require a graft from a donor site, there is less morbidity for the patient. Patients have one wound instead of two.”

Although broad clinical applications of tissue engineering are a few years down the road, Dr. Patrick explained that engineered cartilage and epidermis are already being used in patients. “Because they are relatively avascular tissues, they don’t need a large blood supply to stay alive,” he said. Dr. Patrick listed three main hurdles that researchers need to clear before tissue engineering can be used successfully in more patients. “First, we need cells of some type or a mixture of cells. Then we need a scaffold to give the construct its shape and something for the cells to attach to. These can be very rigid like biodegradable polymer foam or very elastic and resilient like a hydrogel. And then you need to control the microenvironment.” That includes vascularization, which Dr. Patrick described as the “Holy Grail” of all tissue engineering.

One particularly intriguing feature of engineered tissue is that all of the biodegradable materials that make up the scaffold disappear as the tissue grows. “For instance, poly(DL-lactic-co-glycolic acid), or PLGA, naturally degrades into lactic and glycolic acids, which are just normally excreted in urine,” Dr. Patrick said. New pieces of bone have been grown and successfully constructed into a mandible in sheep, and Dr. Patrick and his colleagues have grown new fat tissue in animal models and are working on growing blood vessels and capillary networks. Engineered tissue has as many applications as there are types of tissue in the body, but for now researchers at M. D. Anderson are focusing on adipose tissue for soft tissue and breast reconstruction, bone for mandible reconstruction, and capillary networks for tissue maintenance.

Although he almost certainly never imagined the techniques that are possible today, Gaspare Tagliacozzi, an Italian surgeon, described the plastic surgeon’s job in 1597 as “restoring and making whole those parts which nature or ill fortune have taken away, not so much to delight the eye, but to buoy up the spirit of the afflicted.” In their work at M. D. Anderson, plastic surgeons, bioengineers, and prosthetists are giving new meaning to this old description.

**For more information, contact Dr. Robb at (713) 794-4368, Dr. Jacob at (713) 792-6917, Dr. Lemon at (713) 745-2253, or Dr. Patrick at (713) 794-1247.**
New Replication-Competent Adenovirus Shows

by Kerry L. Wright

I

n gene therapy, viruses are often utilized as vectors for carrying healthy genes into genetically deficient cells, but in some new strategies, the viruses themselves are weapons—designed to seek out, infiltrate, and destroy cancer cells. When pitted against the most vigorous animal model for human gliomas, one of the most powerful new oncolytic viruses, a replication-competent adenovirus called Delta24, completely eliminates tumors.

Based on these striking preclinical results, clinical trials of Delta24 are being planned, and investigators hope they will eventually lead to a more effective treatment for patients with some of the most devastating brain tumors.

“The virus in these particular animal experiments is more powerful than anything we have seen before,” said Juan Fueyo, M.D., an assistant professor in the Department of Neuro-Oncology at The University of Texas M. D. Anderson Cancer Center. Dr. Fueyo and Candelaria Gomez-Manzano, M.D., an instructor in the Department of Neuro-Oncology, are the minds behind the development of Delta24.

While many gene therapy strategies target cells with defects in their p53 pathway, Delta24 targets cells disrupted in the pathway of another master regulator of cell growth, the retinoblastoma (Rb) protein. The new virus contains a 24-base pair deletion in the adenovirus E1A gene, which is essential for viral replication in normal cells but not in cells deficient in their Rb pathways, such as many cancer cells.

In a healthy cell infected with a normal adenovirus, Rb interacts with the virus to prevent its replication—until the virus expresses E1A, which binds to Rb and easily counteracts its inhibitory effects. In contrast, when Delta24 (which has a mutation in E1A) infects a normal cell, E1A cannot overcome Rb’s protective mechanism, so the virus cannot replicate. When the same virus infects a cancer cell that is defective in Rb, however, the virus replicates uncontrollably.

Gliomas, which comprise astrocytomas, oligodendrogliomas, and ependymomas, appear to be particularly well suited for treatment with Delta24. According to Dr. Fueyo and Dr. Gomez-Manzano, more than 90% of the cells in the brain are already quiescent, meaning that the mutant virus should not be able to propagate. At the same time, nearly all glioma cells have disruptions in their Rb pathways, providing the perfect environment for attack by Delta24.

For more than 20 years, patients receiving the conventional treatment for gliomas—aggressive systemic therapy consisting of surgery, chemotherapy, and radiation therapy—have survived an average of only six to eight years with low-grade astrocytomas or oligodendroglomas, three years with anaplastic astrocytomas, and no more than a year and a half with glioblastomas, the highest-grade astrocytoma. Finding strategies to prolong patients’ lives depends on the development of new agents, and successful animal experiments are the first step toward this goal.

When Delta24 was intracranially injected into nude mice containing U-87 human glioma cell-derived tumors, it did exactly what it was designed to do—avoid normal cells while targeting and killing cancer cells. As a consequence, it essentially cured the mice.

“What you could see was just a cavity where the tumor had been and then just these dystrophic calcifications and cystic structures, which is what the body’s cleanup actions would leave,” said Charles Conrad, M.D., an associate professor in the Department of Neuro-Oncology and the clinical medical director of the Neuro and Supportive Care Center at M. D. Anderson.

In mice that were killed midway through the experiment, pathologic assessment of tumor sections by Gregory Fuller, M.D., Ph.D., an associate professor in the Department of Pathology, showed immunohistochemical staining in a three-zone pattern that proved that Delta24 was replicating and spreading through the tumors. Staining of E1A to show viral replication and of the protein hexon to show particle formation identified a central region of necrosis, a middle area of highly infected cells, and an outer area of minimally infected cells. The normal
tissues outside the tumor remained untouched by the virus.

Delta24 is not the first replication-competent adenovirus that has been developed to specifically target cancer cells. The prostate-specific attenuated adenovirus CN706, first developed at Johns Hopkins University Oncology Center, fared well against a human-xenograft mouse model for prostate cancer and is currently in clinical trials. In addition, Dr. Frank McCormick (currently at the University of California at San Francisco) recently developed the ONYX-015 adenovirus, designed to specifically infect cells with mutated p53. Although ONYX-015 showed no toxicity in phase I clinical trials (which is good news for those working on Delta24), it replicated in some cells that were already expressing wild-type p53, partly because it did not function the way its creators had predicted. Concerns that Delta24 may also behave unpredictably are being addressed to increase Delta24's potential for targeted activity in humans.

To increase selectivity, the Delta24 virus contains an extra arginine-glycine-aspartic acid-containing peptide that has a high affinity for alpha(v) integrins, receptors that are expressed much more frequently on the surfaces of glioma cells than on those of normal cells and some other types of cancer cells. Although the virus showed no toxic effects in preclinical studies, no toxicity in mice does not necessarily mean no toxicity in humans, warned Dr. Fueyo. Because adenoviruses almost exclusively infect human cells, many of the toxicity issues could not be directly addressed in the preclinical studies.

"Any time we use some of these viral agents, the immune system can react to them, and they can cause a lot of inflammation and swelling. That is one of the things we are going to be very careful about in the clinical trials," said Dr. Conrad.

A phase I gene therapy trial for malignant gliomas utilizing replication-deficient adenovirus-mediated p53 gene delivery was recently completed at M. D. Anderson. Despite the many differences between the adenovirus used in that trial and Delta24, the surgical procedures used during the trial serve as a paradigm for the Delta24 trial and subsequent gene therapy trials for brain cancer.

"The p53 trial was valuable because it provided us with a novel method for studying tissues," said Frederick Lang, Jr., M.D., an associate professor in the Department of Neurosurgery, who was the trial's principal investigator. Rather thanexcising a tumor from the inside out using suction, as most neurosurgeons do, Dr. Lang and his team actually cut around the entire tumor to remove it.

This way, the virus could be injected through a catheter that remained in the tumor during excision, and the exact point of injection and the precise pattern of propagation of the virus could be determined.

In many ways, the p53 study was a successful gene therapy trial. According to Dr. Lang, the adenovirus vector had minimal toxic effects and produced no viral shedding when injected into the brains of 15 trial participants. In addition, the p53 gene was effectively delivered into glioma cells, where it produced a functional protein. Researchers found, however, that p53 was only delivered within a 5- to 7-mm radius from the point of viral injection.

As is the case in many gene therapy trials, the vector itself may have been effective, but the key to success will be improving delivery. Dr. Lang is currently collaborating with investigators at the National Institutes of Health on a new method called convection-enhanced delivery in which the gene therapy agent is infused (rather than injected) into the brain over several hours to create an electrical wave that will carry the vector farther through the tumor.

For viruses like Delta24, which are already capable of infecting a large area of cells, enhancing selectivity may instead be the key. While Dr. Conrad and Dr. Lang are developing clinical studies of Delta24, Dr. Fueyo and his colleagues continue their preclinical investigations, working on ways to ensure that the virus targets only cells with defective Rb pathways.

"The main thing here is to prove that the Rb pathway in gliomas is a great target for new strategies," said Dr. Fueyo. "Replication-competent adenoviruses like Delta24 are just one way."*

*FOR MORE INFORMATION, contact Dr. Fueyo at (713) 745-3125, Dr. Gomez-Manzano at (713) 792-3563, Dr. Conrad at (713) 745-0187, Dr. Fuller at (713) 792-7935, or Dr. Lang at (713) 792-2400.

See Protocols on next page.
Studies Examine Treatments for Glioma

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for adult patients with malignant gliomas.

- A phase II study of conformal radiation therapy plus interferon alpha-2B and cis-retinoic acid for supratentorial glioblastoma (ID01-005). **Physician:** Mark R. Gilbert, M.D.
  Participants must have recently been diagnosed with supratentorial glioblastoma and must have recovered from the effects of surgery.

- A phase II study of irinotecan (CPT-11) in patients with recurrent malignant glioma (NABTC98-01). **Physician:** W. K. Alfred Yung, M.D.
  Patients with histologically confirmed progressive or recurrent malignant glioma who have measurable lesions with clearly defined margins are eligible.

- A phase II study of irinotecan (CPT-11) in patients with recurrent malignant glioma (NABTC98-01). **Physician:** W. K. Alfred Yung, M.D.
  Patients with histologically confirmed progressive or recurrent malignant glioma who have measurable lesions with clearly defined margins are eligible.

- Phase II evaluation of temozolomide and farnesyl transferase inhibitor (SCH66336) for the treatment of recurrent and progressive glioblastoma multiforme (DM01-258). **Physician:** Mark R. Gilbert, M.D.
  Participants must have histologically proven supratentorial glioblastoma multiforme.

- Phase I trial of intratumoral injection of DTI-015 for recurrent malignant glioma (ID95-115). **Physician:** Samuel J. Hassenbusch, M.D., Ph.D.
  This trial is intended for patients with previously irradiated, recurrent supratentorial malignant glioma who have not had a total resection.

- Phase I/II randomized study of radiation therapy and temozolomide versus radiation therapy and carmustine (BCNU) versus radiation therapy, temozolomide, and BCNU for anaplastic astrocytoma (RTOG98-13). **Physician:** W. K. Alfred Yung, M.D.
  This trial is designed for patients with histologically confirmed anaplastic astrocytoma.

- A phase II evaluation of cetuximab in patients with recurrent glioblastoma multiforme (NCI02-057). **Physician:** W. K. Alfred Yung, M.D.
  Patients must have histologically confirmed recurrent glioblastoma multiforme or gliosarcoma who are not surgical candidates may enroll in this study, as may surgical candidates with radiologically suspected or newly diagnosed disease.

- A phase II study of the safety and tolerability of DTI-015 in patients with recurrent glioblastoma multiforme (ID00-128). **Physician:** Samuel J. Hassenbusch, M.D., Ph.D.
  This study requires histologic proof of supratentorial malignant glioblastoma multiforme with clear evidence of progression.

- Phase I trial of intratumoral injection of DTI-015 for recurrent malignant glioma (ID95-115). **Physician:** Samuel J. Hassenbusch, M.D., Ph.D.
  This trial is intended for patients with previously irradiated, recurrent supratentorial malignant glioma who have not had a total resection.

- Phase I study of temozolomide and farnesyl transferase inhibitor (SCH66336) for the treatment of recurrent and progressive glioblastoma multiforme (DM01-258). **Physician:** Mark R. Gilbert, M.D.
  Participants must have histologically proven supratentorial glioblastoma multiforme.

- Phase I trial of intratumoral injection of DTI-015 for recurrent malignant glioma (ID95-115). **Physician:** Samuel J. Hassenbusch, M.D., Ph.D.
  This trial is intended for patients with previously irradiated, recurrent supratentorial malignant glioma who have not had a total resection.

- A phase I study to assess the histologic effect and safety of preoperative and postoperative infusions of IL13-PE38QQR cytotoxin in patients with recurrent resectable supratentorial malignant glioma (NS01-127). **Physician:** Frederick Lang, Jr., M.D.
  This trial is for patients with histologically confirmed grade 3 or 4 supratentorial malignant glioma.

- Phase I study of temozolomide and farnesyl transferase inhibitor (SCH66336) for the treatment of recurrent and progressive glioblastoma multiforme (DM01-258). **Physician:** Mark R. Gilbert, M.D.
  Participants must have histologically confirmed recurrent glioblastoma multiforme or gliosarcoma who are not surgical candidates may enroll in this study, as may surgical candidates with radiologically suspected or newly diagnosed disease.

- A phase II trial of irinotecan (CPT-11) and temozolomide (Temodal) in patients with recurrent malignant glioma (NABTC99-07). **Physician:** W. K. Alfred Yung, M.D.
  Participants with histologically confirmed supratentorial primary malignant glioma may enroll in this trial if they have measurable lesions with clearly defined margins.

- A phase II trial of STI571 (NSC 716051) in patients with recurrent malignant glioma (NABTC99-08). **Physician:** W. K. Alfred Yung, M.D.
  This trial is designed for patients with intracranial malignant glioma, gliosarcoma, or benign or malignant meningioma.

- Phase I/II trial of CCI-779 in patients with malignant glioma (NABTC01-01). **Physician:** Charles Conrad, M.D.
  This study is designed for patients with histologically proven intracranial malignant glioma who have recurrent disease with evidence of tumor progression.

- Phase I/II trial of R115777 in patients with recurrent malignant glioma (NABTC99-01). **Physician:** Morris D. Groves, M.D.
  Patients must have histologically confirmed primary malignant glioma with confirmed progressive disease.

- Prospective, randomized, double-blind trial of prophylactic phenytoin for patients undergoing resection of primary brain tumors (ID99-320). **Physician:** Frederick Lang, Jr., M.D.
  Patients with untreated glioma and those who have had whole-brain radiation therapy more than four weeks prior to study entry are eligible.

- Prospective study of tumor resection in patients with newly diagnosed glioblastoma multiforme (ID01-261). **Physician:** Raymond E. Sawaya, M.D.
  Participants must have a pathologic diagnosis of glioblastoma multiforme and no prior treatment.

For more information about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.
Denial and Cancer

The word “cancer” evokes many emotions: fear, anger, sadness, helplessness, anxiety. A common protection from anxiety is denial—a psychological defense mechanism in which a person denies the existence of a problem. In most cases, an individual’s initial period of denial is followed by other coping responses, but if denial remains the primary way of handling anxiety, it can have dire consequences. Recognizing the signs of denial in oneself and others is the first step in dealing with this complex problem.

Denial can occur at varying degrees, before and after cancer is diagnosed. Not having recommended screening tests for cancer can be a sign of denial, as can ignoring or not recognizing the early warning signs of disease and not seeking medical attention. For example, an elderly woman might write off a breast lump as just another sign of aging, discounting the possibility of something more serious. Or a person with a skin abnormality or growth might rationalize that because it is not painful or accompanied by other signs and symptoms, it must be benign or not even a tumor at all.

Some patients experience denial after diagnosis. At that point, the inability to accept the reality of their illness can prevent them from following treatment recommendations or returning for follow-up care. It can even lead some patients with cancer to refuse treatment altogether. In addition, denial can be psychologically harmful, interfering with a patient’s adjustment to the cancer diagnosis and illness and affecting the patient’s relationships with others.

Common fears in patients with cancer include disfigurement, dependency on others, and death. Many people are also fearful of invasive procedures such as surgery and harsh therapy. Such fear is normal, and although it can be harmful if left unchecked, it is part of the usual reactions to a cancer diagnosis by patients with cancer and their loved ones.

According to the National Cancer Institute, there are several steps that patients with cancer and their friends and family members can take to meet anxiety and fear head on (see list above).

Above all, know that help is available—from friends, family, volunteers, and health care professionals. No one should have to carry the burden of cancer alone. ☺

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.

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Addressing the Problem of Patients’ Denial

Renato Lenzi, M.D.
Associate Professor, Department of Gastrointestinal Medical Oncology

In common parlance, denial is defined as a refusal to admit the truth of a statement. From a psychological perspective, it is blocking an external reality out of the consciousness. The origin of denial is a prelogical conviction that if something is not acknowledged, it is not happening. Denial has a very important adaptive function in human development. For the infant, denial of an external threat that one is not equipped to physically handle prevents unbearable anxiety. In adult life, temporarily removing from conscious attention the potential for a deadly outcome has provided many a hero with a cool head. Similarly, provided that optimal treatment has been sought and received, denial can be useful in certain patients with cancer by decreasing anxiety and favoring adjustment. Being optimistic when the picture is bleak, “forgetting” negative information, and casting bad news in a better light are all examples of healthy denial.

Denial, however, can just as easily contribute to the most disastrous outcomes when it prevents an individual from taking appropriate adaptive action (such as participating in recommended screening programs or seeking timely medical attention when new symptoms arise). It has been estimated that 25% of patients with clear-cut symptoms of cancer wait more than three months before consulting a physician. Another 8% avoid consulting a physician until they became disabled. While economic and social factors contribute to these delays, denial and denial-like psychological mechanisms such as deferral and disbelief are believed to be responsible for many unfavorable events linked to long delays in seeking medical attention.

Deferral is an absence of adaptive action, although awareness of the illus and of its potential consequences is preserved. Disbelief is often related to the discrepancy between a patient’s experience of their own body (which is not reporting any sign of “malfunction”) and a diagnosis of cancer resulting from testing (for example, a routine screening test).

Health professionals who treat patients with cancer must be able to recognize and appropriately address these mechanisms because no matter how sophisticated, no cancer therapy will benefit a patient who is delaying seeking treatment or who does not comply with medical recommendations.

Identifying and effectively dealing with denial and its mimics are skills very few oncologists have been taught. The Communication Group at M. D. Anderson Cancer Center, which is composed of oncologists, psychiatrists, and behavioral scientists dedicated to research and education in physician-patient communication, has developed algorithms and can provide support and training to help physicians effectively handle difficult medical encounters.

For more information on this and other M. D. Anderson resources regarding difficult communication issues in oncology, please contact Dr. Lenzi at (713) 792-2828.
CLINICAL DISCUSSION:
Breast Cancer Screening & Diagnosis, Part 1

Scope of This Guideline

Presented here are M.D. Anderson's guidelines for breast cancer screening and the institution's approach to the evaluation of abnormal findings on screening mammograms. Part 2 of this discussion, which will appear in the next issue of Compass, will present guidelines for the evaluation of abnormal findings on clinical breast examination.

All of the Breast Cancer Screening/Diagnostic guidelines are available on the M.D. Anderson Web site, along with treatment guidelines. Guidelines for risk reduction in breast cancer are currently being developed.

These guidelines are evidence based where possible; all other recommendations reflect a consensus of expert opinion.

Guidelines for Screening

Overview

"Our screening guidelines are unique," says Dr. Therese Bevers, who directs M.D. Anderson's Cancer Prevention Center. "They differ from standard recommendations that are based solely on patient age in that they are risk based. A breast cancer risk assessment is the fundamental first step to identify women at increased risk whose screening should differ from those at normal risk." There are three targeted groups:

- women who received radiotherapy to the thorax during the second or third decade of life
- women at genetic risk
- women whose history includes lobular carcinoma in situ (LCIS) or atypical hyperplasia

Women who received radiotherapy to the chest area (the most common reason would be for the treatment of Hodgkin's disease or lymphoma) have a 50% greater chance than the normal population of breast cancer development by age 40, the age when routine breast screening is begun. Screening of these women should therefore begin earlier and be done more frequently. Likewise, women who have had proliferative breast

(Continued on next page)
The Gail model, a computerized tool used to estimate breast cancer risk, is based on significant predictors of risk, including a woman's current age, her age at menarche, the number of breast biopsies she has had, her age at the birth of her first child, and how many of her first-degree relatives have or had breast cancer.

Authors' Perspectives

At M.D. Anderson, clinical examination and mammographic evaluation represent the mainstays of breast cancer screening. Risk assessment and risk reduction counseling are important components of breast cancer prevention and are services offered during the screening process. According to Dr. Bevers, "We still encourage regular breast self-examination (BSE) as well, not because there is a proven benefit, but because it helps keep women involved in their own care, and it may help detect interval cancers (those arising between regular screenings). However, BSE received more emphasis in the past in our interactions with women during screening visits than it does now," she says. Now, more time is spent on risk assessment and risk reduction counseling, where benefits have been proven. Identifying women whose risk could be cut in half by taking tamoxifen is an example of such a benefit. Chemoprevention and other risk reduction trials should be considered. More information about clinical trials and protocols available at M.D. Anderson can be found on the Internet at http://www.mdanderson.org/research/

Guidelines for Abnormal Findings on Screening Mammograms

Overview

It is important to differentiate between screening and diagnostic mammography. Definitions, indications, and standards for each are set forth by The American College of Radiology (ACR), which defines screening mammography as a "radiological examination to detect unsuspected breast cancer at an early stage in asymptomatic women. The intent is to separate women into groups with high and low probabilities of breast cancer." Diagnostic mammography, on the other hand, performed under the direct supervision of an interpreting radiologist, implies a request for diagnostic consultation to evaluate a possible abnormality. An exception is that diagnostic mammography is recommended for routine screening in women who have breast implants because special views and compression techniques are required, and the films should be reviewed by a radiologist for quality before the patient leaves. Technologists must have special training to perform this type of mammography.

Usually, a definitive diagnosis does not emanate from a screening mammogram, but rather a report is issued to the referring physician or to the patient in cases of self-referral, assigning the mammogram to a Breast Imaging Reporting & Data Systems (BI-RADS™) category. This system uses terminology consistent with ACR Standards for Communication and provides a standardized way of communicating such results among radiologists, practitioners, and patients. The BI-RADS™ categories outlined are:

ACR-0: An incomplete screening assessment for which additional information is needed.
ACR-1: Negative findings.
ACR-2: benign findings.
ACR-3: indeterminate findings; further assessment is needed.
ACR-4: highly suggestive of malignancy; biopsy is recommended, if feasible.
ACR-5: proven malignancy.
**Breast self-exam is encouraged even though survival benefit has not been proven. Breast self-exam may detect interval cancers between screenings.**

**Criteria for referral for risk evaluation:**

- More than two relatives with breast cancer diagnosed before 50 years of age or ovarian cancer
- One relative with breast and ovarian cancer
- One relative with bilateral breast cancer younger than 50 years
- One male relative with breast cancer
- Ashkenazi Jewish descent and breast or ovarian cancer in the family

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**Diagnostic Evaluation is Indicated**

**ACR-1 (Negative):** Findings normal without need for additional comment

**ACR-2 (Benign):** Negative, but interpreter wishes to comment

**ACR-3 (Probably Benign Finding):** Short-interval follow-up suggested. This category suggests a less than 4% risk of a cancer and is being used less frequently as improved imaging techniques and technologies become available and as data are collected about the efficacy of short-interval repeat imaging.

**ACR-4 (Suspicious Abnormality):** Biopsy should be considered.

**ACR-5 (Highly Suggestive of Malignancy):** Radiologists usually reserve this category for use in cases where there is a high degree of certainty (≥ 90%) that cancer is present. It indicates that appropriate action should be taken.

Patients whose screening mammograms are assigned to category 1 or 2 (negative or benign findings) require no further evaluation and can continue routine screening. This guideline addresses findings in all other categories (0, 3, 4, and 5), which are considered either incomplete (0) or potentially abnormal and for which further diagnostic workup is indicated. Repeat screening mammography is not appropriate at this time; the patient should be referred for diagnostic imaging studies to confirm placement in one of the five BI-RADS® categories that are considered complete.

This evaluation is carried out under the direct supervision of a radiologist and may include special mammographic techniques such as spot magnification or spot compres-
sion, the use of additional views, and ultrasonography. The availability of prior films for comparison is crucial in this assessment: Dr. Steling points out that there is no standard breast anatomy considered normal to all women because normal breast structures vary among individuals, so it is changes—new findings—that are most important. She counsels that in many cases, further studies can be avoided if prior films are available.

This investigation usually proceeds until the radiologist is able to make a definitive assignment to one of the categories considered complete (ACR 1-5). Based on those assignments, the next steps are:

- Return to appropriate screening for ACR 1 and ACR 2.
- Repeat diagnostic mammography in 6 months for ACR 3. An interval shorter than 6 months is not advisable, according to Dr. Steling, because most breast cancers change slowly and “to see no change in 2 months is not good information, whereas no change in 6 months is more significant.” She also notes that this category is used less frequently now with improved techniques and technology and says that these films can often be placed more certainly in category 2 or 4, especially if previous films are available.
- Tissue diagnosis for ACR 4 and ACR 5. “We try to diagnose our cancers by image-guided needle biopsies when possible,” says Dr. Bevers, “and we’re able to do that about 90% of the time, either using ultrasound-guided fine-needle aspiration or core biopsy or stereotactic core biopsy.” These techniques are preferred over excisional biopsy for several reasons: they are less disruptive of breast tissue and cause less deformity; they leave more treatment options available, including sentinel lymph node biopsy; and they allow a woman to know her diagnosis in advance of choosing treatment options.

**Authors’ Perspectives**

When your patient has an abnormal mammographic report:

- Patients are usually anxious; a structured approach often helps the clinician alleviate a patient’s fears.
- Be thorough, to minimize repeat studies.
- Remember to evaluate the other breast.

Dr. Steling notes that about 10% of patients are recalled for further study. Of every 1,000 previously unscreened women, approximately 90 to 100 women will require further workup, approximately 11 will require biopsy; and about 4 will be found to have cancer.

“The importance of prior films for comparison cannot be overstressed. A pearl from Dr. Steling: patients frequently forget where their previous mammograms were done—particularly if they have moved to another city—but they rarely forget their physician’s name and can be counseled to contact his or her office to obtain the name and contact information of the facility. When Dr. Steling’s patients are preparing to relocate to another city, she advises them to write for their films after they are settled in the new location to avoid having them lost in the move.

Patients who develop a palpable mass or other symptoms between screenings should be referred for diagnostic (not screening) mammography. Dr. Steling advises physicians to be especially aware of this, as delays may increase the number of repeat studies, cause delayed or missed diagnoses, and represent a legal liability for physicians. Diagnostic mammography is also indicated for patients whose screening mammography report places them in BI-RADS™ categories 0, 3, 4, or 5. Continue investigating until all findings are concordant. Both of our experts agree that the most critical aspect of evaluating breast abnormalities is to ensure that all findings match: that imaging (including ultrasonography) interpretations, pathologic analysis, and clinical findings are all in agreement and in fact explain each other. If this is not the case, investigation should continue. For example, if calcifications are seen on a mammogram, but the pathology report indicates fibrocytic changes without calcification, then the original question is not answered. “Are pathology findings concordant with imaging studies? Does the biopsy result directly answer the questions raised by the abnormal mammogram? Do all of these match the clinical findings? If not, then don’t stop there,” says Dr. Bevers. A benign pathology study result following an ACR-5 mammogram is not concordant, she says, and is likely to represent a sampling error rather than a benign condition.

**References & Suggested Reading**

American College of Radiology (ACR). Standards for Diagnostic Mammography, 1/1/99

American College of Radiology (ACR). Standards for Screening Mammography, Amended 1995 (Res 24, 53)

