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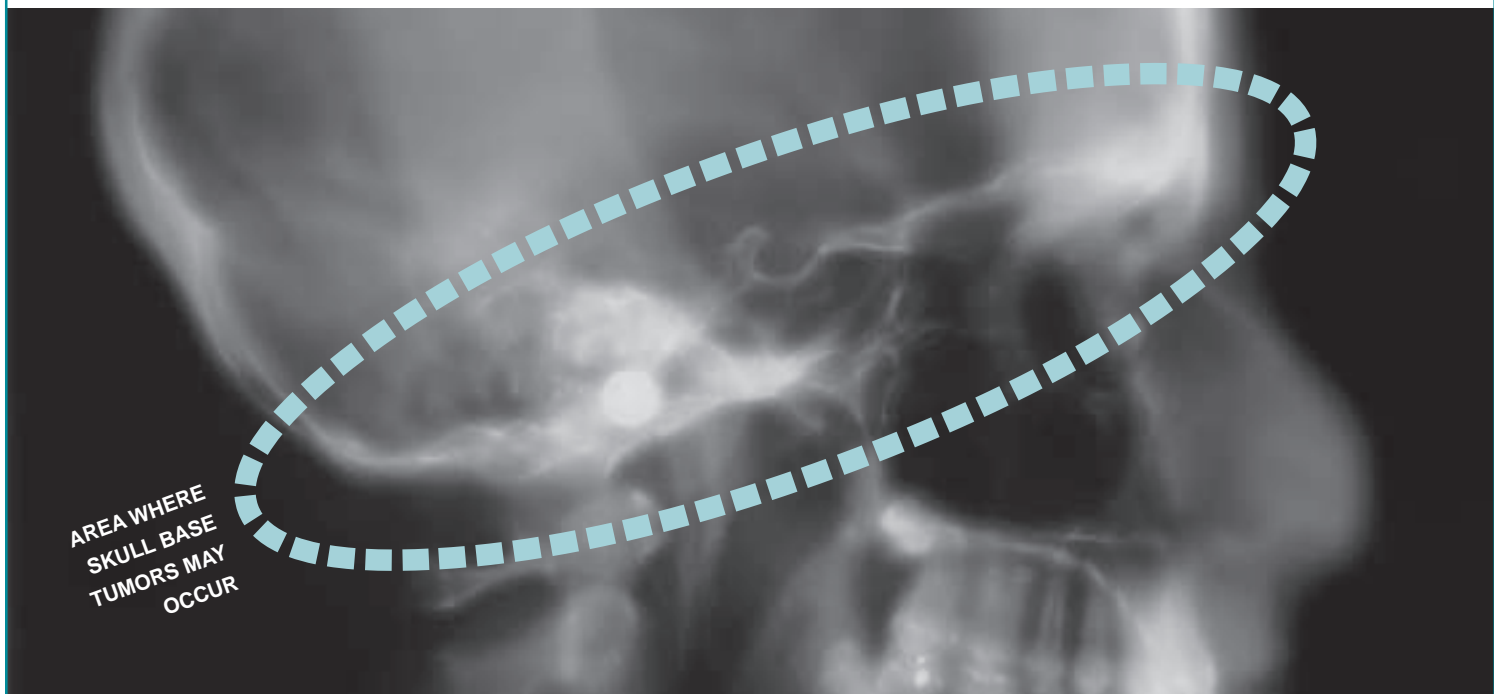
REPORT TO PHYSICIANS NOVEMBER 2006 Vol. 51, No. 11

Oncology

Treating Skull Base Tumors

by Sunni Hosemann

Highly specialized, collaborative expertise is key in treating these rare tumors.



At the base of the skull lies an intricate scaffolding upon which the brain rests. As the floor of the cranium, its nooks and hollows are marked by various sized openings through which large vessels and critical nerves—including the brainstem itself—traverse on their way to and from the brain. Tumors that grow here can originate from any of the tissue types nearby, such as brain, nerve, sinus, or bone. These tumors lie deep within the head, and they can insinuate themselves in the most difficult ways—hiding in the hollows, enmeshing with tissues, and twisting themselves around critical neural and vascular structures. *(Continued on next page)*

THE UNIVERSITY OF TEXAS
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Treating Skull Base Tumors

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Unique for their diversity as well as their location, dozens of different kinds of tumors arise in the skull base, and some are very rare. They include meningiomas, neuromas, angiomas, schwannomas, melanomas, and several kinds of carcinomas and sarcomas, as well as pituitary tumors, bony tumors, cysts, fibrous lesions, and a host of others.

Their treatment requires the expertise of many: for a start, it's best to have surgical, medical, and radiation oncologists who specialize in these kinds of tumors. To fully optimize outcomes

beyond survival, including restoration of form, function, and quality of life, the services of a host of other medical and rehabilitation specialties are necessary.

Not all skull base tumors are cancers. "At least half of the patients we see have benign tumors," said Franco DeMonte, M.D., a co-director of the Skull Base Tumor Program at The University of Texas M. D. Anderson Cancer Center and a professor in the Department of Neurosurgery. The malignant tumors require treatment—surgery plus chemotherapy

or chemoradiation given neoadjuvantly or adjuvantly.

"Usually, we can tell by imaging studies whether a tumor is benign or malignant," said Dr. DeMonte. The malignant tumors must be biopsied: "We must have accurate pathology," he said, "and for that we rely on neuropathologists and head and neck pathologists who are specialized in this area." Some of the benign tumors can be left alone and serially monitored; others can grow and impinge on vital structures and must be treated.



Dr. Ehab Hanna, holding a flexible laryngoscope, and Drs. Franco DeMonte, Paul Gidley, and Michael Kupferman (l to r) collaborate on how to treat skull base tumors with bi-directional access.

Treatment advances

One of the most significant strides forward in skull base tumor treatment has come simply from collaboration. Disease below the skull base has traditionally been the purview of head and neck surgeons, while neurosurgeons usually dealt with everything above it. Collaboration between these two disciplines, little more than a decade old, was necessary to best treat these tumors, which occupy the border between the two. "These tumors require bi-directional access—the combined expertise of those comfortable with intracranial and extracranial approaches," said Ehab Y. Hanna, M.D., a co-director of the Skull Base Tumor Program and a professor in the Department of Head and Neck Surgery. That collaboration has resulted in a unique subspecialty; members of The North American Skull Base Society come from both disciplines.

“These tumors are often found in ‘corners’ and near intricate structures, making intraoperative imaging especially useful for endoscopic procedures.”

— Dr. Franco DeMonte

Surgical treatment of skull base tumors has dramatically advanced through the use of minimally invasive techniques. In the past, operating on these tumors involved major incisions and consequent facial scarring. “An extensive external approach meant a large facial incision and displacement of bone—essentially a temporary disassembly of the bony structures of the face,” said Dr. Hanna. “These operations could be extensive: 10- to 12-, even 14-hour, surgeries with prolonged hospital stays.”

Minimally invasive surgery allows access to the tumor via an endoscope through existing cavities, like the nose, significantly reducing the length of surgery and of recovery. “This factor alone translates into a better functional outcome,” said Dr. Hanna, who was recruited to the program for his rare expertise in the use of minimally invasive techniques for tumors of the skull base.

These techniques are constantly improving, meaning that more and more tumors can be approached this way. Other new technologies are emerging that also bear great promise for skull base tumor treatment.

“The da Vinci Surgical System, a new robotic surgical technology, is one of the avenues we’re interested in adapting for skull base surgeries,” said Randal Weber, M.D., professor and chair of the Department of Head and Neck Surgery. The system, currently in use in other types of surgery, will require modifications and refinements for this application. The da Vinci system has two attributes that should prove critically useful in skull base tumor surgeries: high-definition visualization and instrumentation that behaves like a super-dextrous wrist that can operate in very confined spaces. The visualization is provided by a fiberoptic stereoscopic camera system, which allows the surgeon to see the three-dimensional operative field in full color, magnified, and at very high resolution. The system’s computer translates the surgeon’s hand movements to robotic arms that operate very fine instruments. According to Dr. Hanna, “The advantage of da Vinci is that the instrument

Specialties

Involved in the Skull Base Tumor Program

- Head and Neck Surgery
- Neurosurgery
- Neuro-Otology
- Neuro-Oncology
- Plastic and Reconstructive Surgery
- Ophthalmology and Neuro-Ophthalmology
- Head and Neck Radiation Oncology
- Pathology, Head and Neck Neuropathology
- Head and Neck Medical Oncology
- Oncologic Dentistry and Prosthodontics
- Diagnostic Imaging and Radiation
- Proton Therapy
- Rehabilitation Services
- Audiology
- Speech, Language, and Swallowing Therapies
- Neuropsychology
- Nutrition
- Occupational Therapy
- Physical Therapy
- Behavioral Psychology



Dr. Ehab Hanna (l) and Dr. Franco DeMonte (far right) believe skull base tumors are best treated in a specialized program with a concentration of experience.

used can be very small, meaning that the size of the access can be small, and the robotic arm has free movement in all axes, allowing you to go around corners, behind vessels.”

“The BrainSUITE at M. D. Anderson is another development that will be of decided value for some of the surgical cases we see,” said Dr. Hanna. BrainSUITE’s state-of-the-art equipment gives surgeons a capability critical to removing intracranial tumors: high-intensity intraoperative magnetic resonance imaging. Skull base tumors present some of the same challenges to the surgeon that many brain tumors do: surgeons must chase the farthest reaches of the tumor, calculating how deep to go

to completely resect it without damaging critical structures nearby. Without intraoperative imaging, surgeons must rely on preoperative images and their own calculations, which must also account for positional shifts that typically occur during brain surgery. “In addition, these tumors are often found in ‘corners’ and near intricate structures,” said Dr. DeMonte, “making intraoperative imaging especially useful for endoscopic procedures.”

Proton therapy, newly available at M. D. Anderson, is another new technology that is expected to benefit many patients with skull base tumors. “We expect skull base tumors to be one

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Treating Skull Base Tumors

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“These tumors require bi-directional access—the combined expertise of those comfortable with intracranial and extracranial approaches.”

— Dr. Ehab Hanna

of its most important applications,” said Dr. DeMonte. Proton therapy is more advanced than standard radiation therapy because the exact location at which the proton beam will deposit its energy can be programmed in three dimensions, meaning that it can be aimed at deep tumors and contoured to their shape. Healthy adjacent and intervening tissues go unharmed.

This precision will be a distinct advantage with the types of tumors found in the skull base. Consider a tumor near the optic chiasm: “With surgery, we can come close to it—perhaps 2 mm—and then follow with proton therapy to perhaps destroy that remaining 2 mm. That’s not possible with conventional radiation therapy,” said Dr. Weber. Three protocols for skull base tumors are currently in development for proton therapy, targeting tumors of the sinus cavity and nasopharynx and bony tumors of the skull base.

This group of physicians believes that whether benign or malignant, rare or common, tumors are best treated in a specialized program where there is a concentration of experience, as well as rehabilitation resources for the critical path to a quality life for patients, and that just such an environment exists at M. D. Anderson. “I have never worked in a place that had this gamut of services,” Dr. DeMonte said. “This is our focus: it’s all we do.” ●

FOR MORE INFORMATION on the Skull Base Tumor Program, call 1-800-392-1611 (option 3).

IN BRIEF

Herceptin’s Cardiac Toxicity Reversible

The first study to look at the long-term use of trastuzumab (Herceptin) in metastatic breast cancer patients outside a clinical trial found a higher incidence of cardiac toxicity than clinical trials of the drug have reported to date, but it also concluded that for most patients, the damage could be reversed with treatment.

The study, published in the September 1 issue of the *Journal of Clinical Oncology*, weighs the drug’s risks and benefits and concludes that use of Herceptin in patients with metastatic breast cancer “is an acceptable risk,” said the study’s lead author, Francisco J. Esteva, M.D., Ph.D., an associate professor in the Department of Breast Medical Oncology at M. D. Anderson Cancer Center.

In clinical trials testing Herceptin in combination with chemotherapy, 10% to 26% of patients experienced cardiac toxicity, depending on the treatment protocol. That led to a Food and Drug Administration warning in 2003 that Herceptin use can result in congestive heart failure or ventricular dysfunction.

According to Dr. Esteva, before this study, no one had looked at what happened to patients treated in a clinic, outside of an organized trial, after they used Herceptin for a year or longer. “We often give it for several years if patients are responding to the treatment, so we set out to quantify the risks,” he said.

“We found that the drug substantially prolongs survival, and while we also found substantial cardiac toxicity, we also discovered that this side effect can be successfully treated, which was not clearly known before this study,” said Dr. Esteva. “If the cardiac side effects of Herceptin treatment can be managed, the drug is safe to use.”

In most patients who developed cardiac toxicity on this study, the effects were reversed by discontinuing Herceptin and administering beta-blockers and ACE inhibitors. After the damage was repaired, patients could resume Herceptin treatment. Dr. Esteva

pointed out that these results do not apply to use of the drug in patients with early-stage disease, for whom the risks of cardiac toxicity may outweigh the benefits of Herceptin.

Dr. Esteva stressed that patients with advanced breast cancer should receive a baseline cardiac assessment before the drug is used and then follow-up care by a cardiologist. “This is an accurate representation of clinical practice in that patients often have important comorbidities that place them at increased risk for cardiotoxicity,” Dr. Esteva said. “It illustrates the need for good cardiac care for advanced breast cancer patients.”

Nanoparticles Target Ovarian Tumors

A molecular “off” switch packaged in a liposome penetrates deeply into ovarian tumors, stifling a troublesome protein and drastically reducing the size of tumors, researchers at M. D. Anderson Cancer Center report in the August 15 edition of *Clinical Cancer Research*.

The experiment in mice demonstrates a potent delivery system for short interfering RNA (siRNA) to attack cancer, said senior authors Anil Sood, M.D., a professor in the Departments of Gynecologic Oncology and Cancer Biology, and Gabriel Lopez-Berestein, M.D., a professor in the Department of Experimental Therapeutics at M. D. Anderson. “Short interfering RNA is a great technology we can use to silence genes; it shuts down production of proteins that promote survival of ovarian cancer cells,” Dr. Sood said. “It works well in the lab, but the question has been how to get it into tumors.”

Short pieces of RNA don’t make it inside a tumor without being injected directly, and injection methods used in the lab are not practical for clinical use. To address that problem, the research team took siRNA and packaged it into neutral liposomes, nanoparticles that can penetrate deeply into tumors.

Getting the siRNA inside tumor cells is important, Dr. Sood said, because the targeted protein, focal adhesion kinase (FAK), is inside the

cell rather than on the cell surface where most proteins targeted by cancer drugs are found. “Intracellular targets like FAK, which are difficult to reach with a drug, can be attacked with this therapeutic liposomal approach,” Dr. Sood said.

Mean tumor weight in mice receiving the FAK-silencing liposome dropped 44% to 72% compared with mice in the control groups. When researchers combined the FAK-silencing liposome with the drug docetaxel, tumor weight reduction was boosted to the 94% to 98% range.

These results also held up in experiments with ovarian cancer cell lines resistant to docetaxel and cisplatin. The treatment may also show promise for other cancers in which FAK is overexpressed.

These findings suggest that the therapeutic liposomal FAK siRNA in combination with docetaxel or cisplatin may have promising clinical applications, even for patients with chemotherapy-resistant tumors.

Multi-Drug Approach Required for Acute Myelogenous Leukemia

The road to better treatment for the most common form of adult leukemia will require blocking multiple molecular pathways that fuel the disease, researchers at M. D. Anderson Cancer Center report in the October 1 edition of the journal *Blood*.

The research team examined blood and bone marrow samples from 188 adults with acute myelogenous leukemia (AML) and then followed the patients’ progress to gauge the cumulative impact of a trio of cell-signaling chain reactions on the disease.

The research team looked at activation of three components, one from each pathway, in the leukemic blasts found in newly diagnosed patients. Activation of each component—PKCa, pERK2, and pAKT—had an adverse effect on the patient’s prognosis that was independent of other traditional prognostic factors. Their cumulative impact was greater than simply adding

their individual effects would suggest, the research team found.

“We found that the more of these pathways that are active in a patient, the worse their prognosis,” said first author Steven Kornblau, M.D., associate professor in the Department of Stem Cell Transplantation.

Patients who had none of the three molecular cascades active had a median survival time of 78.6 weeks. For those with one highly active pathway, median survival was 57.9 weeks. With two, it was 42.3 weeks. Patients with high activation of all three pathways had a median survival time of just 23.4 weeks.

“Targeting just one of these pathways won’t be effective because we also found that they cross-activate each other; they essentially cover for each other,” Dr. Kornblau said. “New therapies will have to target multiple pathways to be effective.”

This presents several challenges to discovering a successful treatment for AML, the research team noted. New drugs are typically evaluated individually during development, so a medication that blocks one of these pathways is likely to fail to treat AML by itself. It would probably be discarded as a single therapy when it could become part of a multiple-drug attack on the disease.

Race Influences Survival in Breast Cancer

African-American women with breast cancer are more likely to have larger, later-stage tumors that are more difficult to treat than Hispanic and Caucasian women who receive the same treatment, according to two independent series of clinical trials examined by researchers from M. D. Anderson Cancer Center.

The analysis, published online October 23 by *Cancer*, indicates that race is associated with unfavorable tumor biology, which, along with other factors, likely contributes to the lower rate of breast cancer survival among African-Americans. This group was more likely to have estrogen-receptor negative tumors, which are considered more difficult to treat.

“These findings should prompt additional research on how we can improve outcomes for African-American patients by understanding and addressing tumor biology,” said first author Wendy Woodward, M.D., Ph.D., assistant professor of radiation oncology at M. D. Anderson. “Not all African-American women will have worse survival prospects, but there are probably subsets of patients for whom we could be doing something better.”

African-American women are less likely than Caucasian women to have breast cancer but are more likely to die from it. Many factors have been implicated in this disparity, the researchers note, including access to health care and screening, differing treatments, socioeconomic status, and racial bias. However, they doubt socioeconomic factors could fully explain differences in survival rates because Hispanic and African-American women have similar socioeconomic status in M. D. Anderson’s patient referral area.

“These findings should prompt additional research on how we can improve outcomes for African-American patients by understanding and addressing tumor biology.”

— Dr. Wendy Woodward

The study looked at 2,140 breast cancer patients who were treated in two prospective series of clinical trials at M. D. Anderson involving use of doxorubicin before and after a radical or modified radical mastectomy.

A multivariable analysis that took into account age, estrogen-receptor-negative status, primary tumor size, and whether the disease had spread to the lymph nodes showed that African-American race is an independent factor in a lower overall survival rate. “We interpret these data as suggesting that intrinsic biological differences in the disease and response to treatment among racial groups contributed to the poorer overall survival rates seen in the African-American cohorts,” the researchers concluded.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC), an extremely rare, fast-growing, and lethal form of breast cancer that can spread in just a few weeks, is often mistaken for something other than breast cancer, such as a rash or infection. All aspects of treating IBC—including staging, diagnosis, and therapy—are vastly different from other breast cancers.

IBC is more likely to be misdiagnosed, and ultimately diagnosed after the disease has metastasized, said Massimo Cristofanilli, M.D., associate professor in the Department of Breast Medical Oncology at M. D. Anderson Cancer Center.

The extremely aggressive disease represents 1% to 2% of newly diagnosed invasive breast cancers in the United States. Unlike other breast cancers that present as a lump, IBC's symptoms are unique and include redness, swelling, and warmth in the breast; skin that is reddish, purple, or bruised; and skin that has ridges and/or appears pitted like an orange. Other symptoms can include burning, aching, or tenderness, an increase in breast size, and an inverted nipple.

The median age range of IBC patients is between 45 and 55 years old. The 5-year median survival rate is approximately 40%. "There are a number of reasons for such a disappointing survival outcome—a delay in diagnosis because it is often mistaken for a rash, the lack of expertise in treating IBC because it is so rare, and the relative resistance the disease has to standard chemotherapeutic agents," said Dr. Cristofanilli.

Detecting and treating IBC

"Because IBC usually does not occur in the form of a lump and instead spreads throughout the breast tissue, it is very difficult to detect the disease with a mammogram," said Dr. Cristofanilli. Magnetic resonance imaging and biopsies generally cannot accurately diagnose IBC either. However, surgical biopsy and positron emission tomography (PET) can be used. In the near future, PET scans could be one of the most important diagnostic/staging tests for IBC. "Though still under study, we have found that with PET scans, we can see more of the IBC, including lymph nodes far from the breast, which will allow us to determine if there is metastatic disease at the time of diagnosis," said Dr. Cristofanilli.

Current treatment for IBC includes chemotherapy, surgery, radiation, targeted therapy, and/or hormonal therapy when appropriate. In early preliminary studies, the hormonal therapy lapatinib (Tykerb) has shown promise for IBC patients whose tumors express the HER-2 gene. M. D. Anderson is using drugs like trastuzumab (Herceptin) or lapatinib in a subset of IBC patients that have the HER-2 gene. Researchers are focused on finding ways to eliminate microscopic disease to prolong survival in IBC patients. "We hope to conduct future lapatinib studies in this clinic and determine if the drug works by itself, with chemotherapy, or with several chemotherapies," Dr. Cristofanilli said.

A new clinic especially for IBC

In an effort to better understand the complexities of IBC and to improve the

Inflammatory breast cancer symptoms can include:

- redness, swelling, and warmth in the breast
- skin that is reddish, purple, or bruised
- skin that has ridges and/or appears pitted like an orange
- burning, aching, or tenderness
- increase in breast size
- inverted nipple

outcomes for women with the disease, M. D. Anderson has established the first clinic in the world dedicated to the treatment and research of IBC. Exploring new treatments for IBC will be a priority of the clinic, said Dr. Cristofanilli.

Under the co-direction of Dr. Cristofanilli and Thomas Buchholz, M.D., a professor in the Department of Radiation Oncology, the clinic plans to see 60 to 80 new patients annually, more than double the number it currently treats.

"The primary goal of both the clinic and the research program is to finally understand why this disease is different, why it is so resistant to treatment, and ultimately, to develop therapies that improve the well-being of women with this very rare form of breast cancer," said Dr. Cristofanilli.

"The scientific community needs a comprehensive clinic and research program in order to make significant progress in the overall prognosis of women with IBC. There are so few cases of this disease, and they are scattered throughout the world. We will collect appropriate serum and tissue, look at gene expression, and gather other pertinent biological information in hopes of finally developing treatment guidelines for IBC," said Dr. Cristofanilli. ●

FOR MORE INFORMATION, call M. D. Anderson's Information Line, 1-800-392-1611, option 3.

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— Dr. Massimo Cristofanilli





On the Job with Cancer

According to the American Cancer Society, approximately 1.4 million people will be diagnosed with cancer in the United States this year. Many of these people will be adults who will have to decide whether they can continue working while undergoing treatment.

Coping with cancer and the side effects—and after-effects—of its treatments can be difficult, and it is not uncommon for people in this situation to worry about losing their jobs. As with other illnesses that limit a person's ability to do major life activities, cancer may meet the definition of a disability under the Americans with Disabilities Act (ADA).

Cancer as a disability

The ADA is a federal law that prohibits discrimination on the basis of disability in the workforce. The law defines “disability” as a physical or mental impairment that substantially limits one or more major life activities, a record of such an impairment, or being regarded as having such an impairment. Specific conditions and diseases are not defined, but cancer qualifies as a disability if the disease itself or the side effects of treatment substantially affect your ability to perform major life activities, such as caring for yourself, walking, interacting with others, or concentrating. Cancer survivors who experience long-term after-effects of cancer or its treatment, such as severe fatigue, depression, or cognitive functioning problems, may also be considered as having a disability. However, cancer may not be considered a disability unless the effects are permanent or long term.

Talking with your employer

Deciding whether or not to tell your employer you have cancer is a personal

decision. However, you can be protected under the ADA *only* if your employer knows about your disability. Thus, it's important to let your supervisor know, if you think your cancer or cancer treatment is going to affect your ability to work or your ability to carry out daily activities. The ADA limits your employer's right to inquire about the specifics of your medical condition, but you may still need to supply documentation from your doctor. Employers can ask about your medical condition if they believe that it will affect your ability to safely do your job or if your condition may affect others in your workplace.

The law does not require your employer to lower job standards to accommodate your disability; you will still be required to perform the essential functions of your position. However, your employer must provide “reasonable accommodations” to help you perform those essential functions.

Reasonable accommodations

The ADA defines “reasonable accommodations” as making the workplace readily accessible to and usable by employees with disabilities. Such accommodations aren't necessarily expensive or elaborate. For someone with cancer, they might include job restructuring, part-time or modified work schedules, telecommuting arrangements, assistive devices, rest breaks during the day, modifications of policies, and other similar accommodations. As long as it does not present a financial or “unique” hardship for your employer, you can expect them to make accommodations such as those listed above. However, reasonable accommodations do *not* include providing additional insurance coverage or paying for medical treatments.

Employees undergoing cancer treatments may consider requesting modified work schedules to accommodate their treatment regimens and medical appointments. A modified work schedule or part-time telecommuting arrangement is also a good idea if severe fatigue is one of the side effects of



As with other illnesses that limit a person's ability to do major life activities, cancer may meet the definition of a disability under the Americans with Disabilities Act (ADA).

treatment. It's good to know as much as possible about how your treatment and its side effects may affect you and to research alternatives that may work well for both you and your employer.

Additional resources

There are a number of other options that may be available to employees with serious health problems, such as the Family and Medical Leave Act, long- and short-term disability insurance, variable work schedules, and others. Your human resources department may be able to help you with additional information or help you obtain the reasonable accommodations you need. For more information on the Americans with Disabilities Act, call the ADA Information Line at 1-800-514-0301. You can also find more information from the following: Job Accommodations Network, www.jan.wvu.edu; and Cancer Legal Resources Center, (866) 843-2572. ●

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.

November 2006

M. Gonzales

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DiaLog

Helical CT Screening: Does It Affect Lung Cancer Outcome?

Reginald F. Munden, M.D., Professor, Department of Diagnostic Radiology



Despite tremendous efforts over the past several decades, the overall 5-year survival rate for lung cancer is below 14%. This is partly because a significant number of lung cancers are not detected at an early stage. Recent advances in imaging include helical computed tomography (CT), which allows the whole chest to be scanned rapidly in a single breath-hold, thus greatly improving the ability to detect small cancers. For this reason, there is much interest in applying helical CT to lung cancer screening.

However, low-dose CT screening for lung cancer has proven to be a complex and controversial topic. The fundamental goal of screening is to detect disease at a stage when it can be cured. The screening test must carry low risk; be accurate, with an acceptable level of “false alarms”; be easily obtained; and be cost effective. There have been a number of studies of CT screening for lung cancer, but there is still much controversy as to whether helical CT screening meets these criteria.

In a recent study in the *New England Journal of Medicine*, Dr. Claudia Henschke and colleagues estimated a 10-year survival rate of 88% in patients who had stage I lung cancer detected by helical CT. To date, the

results of all of these screening studies are very exciting, but so far they have shown only that helical CT can detect small lung cancers—not necessarily that this will affect the patient’s outcome.

The controversy is predominantly in two areas: the reduction in lung cancer mortality and the number of false-positive CTs (or false alarms). Studies indicate a longer survival time with CT screening, but this may be due to a longer lead time bias in which patients are diagnosed earlier—but die at the same time they would have if diagnosed later. In screening trials, it is mortality that truly reflects a screening test’s effectiveness, because the data are not subject to lead time biases.

The second major issue with helical CT is that many false-positive results will occur because of the test’s sensitivity. Several of the studies have reported that up to 70% of the people screened had abnormalities that needed further medical evaluation, few of which were subsequently found to be of clinical significance. In order for this level of potential false-positive findings to be acceptable, there has to be a significant benefit (i.e., reduced mortality) to the screening test.

More definitive data may be available in just a few years. The National Cancer Institute is sponsoring a large randomized controlled study to evaluate helical CT in lung cancer screening compared with chest x-ray. This study should be completed in 2009 and answer the question of whether screening with helical CT is effective in reducing lung cancer mortality. ●

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Made possible in part by a gift from the late Mrs. Harry C. Wiess.

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