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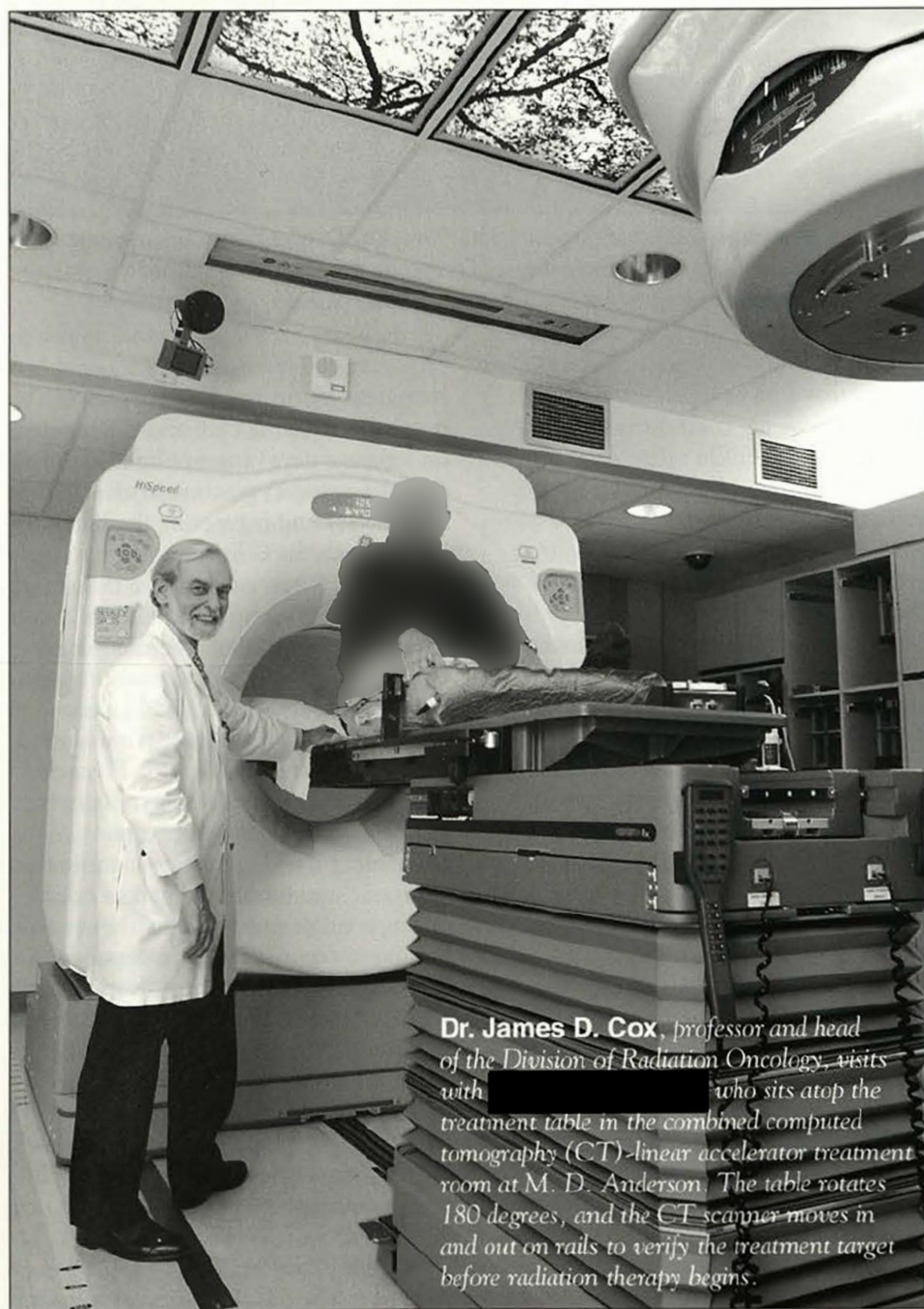
Advances in Imaging Lead to More Targeted Radiation Treatments

by Dawn Chalaire

In the practice of radiation oncology, the eternal question is how to treat a tumor most effectively while minimizing the exposure of normal tissues to radiation.

Part of the answer lies in increasing the accuracy and precision of dose calculations and treatment delivery, but the first step is getting the best possible picture of the tumor. Beyond knowing precisely where a tumor is and its size, shape, and viability, new imaging techniques are making it possible to “see” the molecular makeup of the tumor and its metabolic activity.

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Dr. James D. Cox, professor and head of the Division of Radiation Oncology, visits with [redacted] who sits atop the treatment table in the combined computed tomography (CT)-linear accelerator treatment room at M. D. Anderson. The table rotates 180 degrees, and the CT scanner moves in and out on rails to verify the treatment target before radiation therapy begins.

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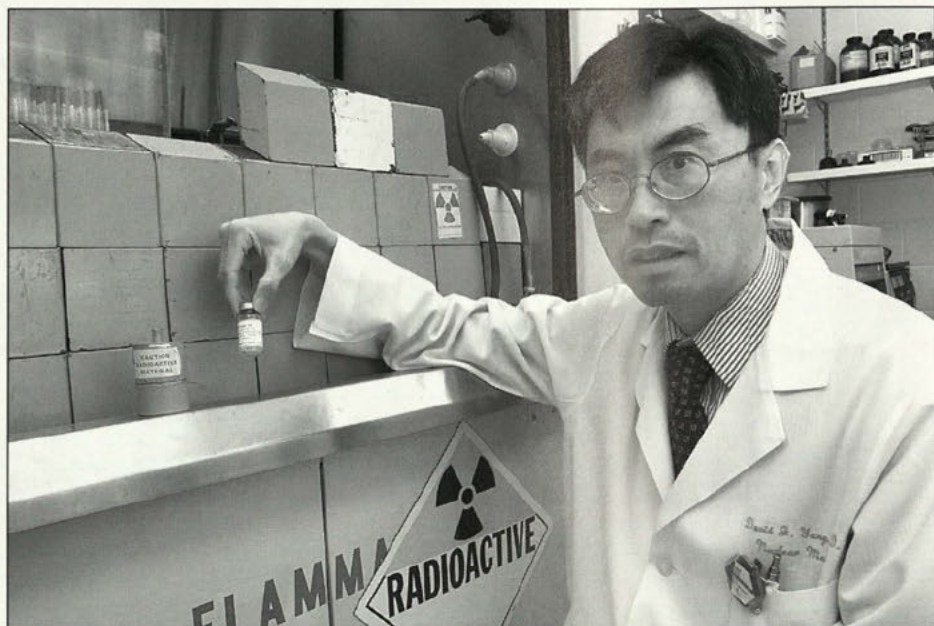
Advances in Imaging Lead to More Targeted Radiation Treatments

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"The images that we want to get are the functional and dynamic indicators of the molecular components of the tumor. Not just the anatomic tumor, not just the lump, but what is in the lump metabolically and in terms of these molecular targets," said James D. Cox, M.D., professor and head of the Division of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center.

Most radiation therapy treatment planning is based on computed tomographic (CT) images that show the tumor location, the distances from the center of the tumor to the surface of the skin, and the composition of the tumor and surrounding tissues. CT and, more recently, magnetic resonance imaging (MRI) can provide very accurate images of the anatomical elements of a tumor. But CT and MRI cannot, for example, differentiate between malignant tumor, edema, and radiation necrosis. According to Dr. Cox, "the real advance" in tumor imaging occurred with the development of positron emission tomography (PET). Using radioisotope labeling, PET images reveal where a tumor is metabolically active by highlighting the uptake of glucose. Thus, the differences between active and necrotic tumors and between malignant and benign lesions are visible on PET images.

"Working with our colleagues in Diagnostic Imaging, we have deter-



Using the inexpensive radioisotope technetium-99m, Dr. David Yang, an associate professor in the Department of Experimental Diagnostic Imaging, has developed a technique for imaging molecular targets that could be used to select patients for treatment with radiosensitizers.

mined that PET is valuable, both in terms of showing tumors that have spread when we didn't think the tumors had spread and in helping us plan the radiation treatments better," Dr. Cox said. "In some cases, we've found that what we thought was normal by CT didn't show the whole picture. So the PET showed more because it allows physicians to visualize metabolic rather than anatomic changes. We also found that what seemed to be all tumor on the

CT scan was actually only partly cancer, and the rest of it was maybe the collapse of the lung or some other thing that looked like the tumor."

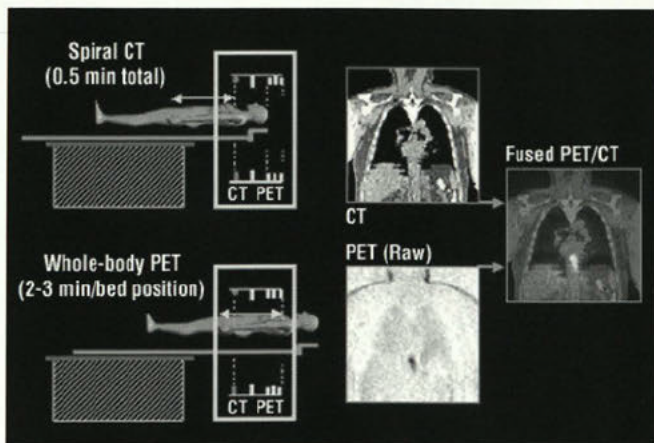
Although PET imaging can provide a very accurate picture of metabolically active areas, its ability to show anatomic features is limited. As a result, a few institutions have begun to combine PET images with CT scans used for

treatment planning. This process involves acquiring PET and CT images on separate days (attempting to replicate the patient's position as closely as possible) and registering the PET images with the CT scans.

"This has been an arduous task that requires careful coordination and cooperation among key people in Radiation Oncology, Radiation Physics, and Diagnostic Imaging," said Ken Forster, Ph.D., an assistant professor in the Department of Radiation Physics.

Recently, an alternative to registering PET and CT images became available. PET-CT scanners combine anatomic and functional images taken during a single procedure, without having to reposition the patient between scans. Two scanners that combine rapid, advanced CT and PET imaging will soon be available at M. D. Anderson for diagnosis and radiation treatment planning. Both scanners will have large-bore openings to accommodate patients who must wear immobilization devices.

"When we use this for radiation treatment planning, we can place the patient in the position we would use for



PET-CT scanners rapidly combine anatomical and functional images. (Graphic courtesy of GE Medical Systems and the University of Zurich.)

treatment—special body case, arms in a particular position, etc. This will permit us to plan more precisely to irradiate the areas that are metabolically abnormal and still have the detailed anatomy of the normal structures,” said Dr. Cox.

Techniques that reveal the molecular makeup of tumors offer an even more intimate view. Molecular imaging techniques (PET, PET-CT, and single-photon emission CT [SPECT]) are being developed to monitor tumor response to treatment, make differential diagnoses, and predict response to therapy. David Yang, Ph.D., an associate professor in the Department of Experimental Diagnostic Imaging, is developing a novel method of imaging molecular markers that makes use of an inexpensive radioisotope and widely available, low-energy gamma ray imaging machines.

“We now have a way of labeling different biomolecular markers, with technetium and with ethylene dicycysteine as a chelator, using a technology that is universal,” Dr. Yang said. “We can put on a label and use this in patients. Other techniques only allow for labeling with fluorescence and things that you can see under a microscope but that may not have sufficient depth penetration to be seen in the patient.”

In addition to assessing molecular targets, technetium-99m might be useful in planning internal targeted radionuclide therapy with rhenium-188-labeled agents. Both technetium-99m and rhenium-188 emit gamma rays, so estimates of patient dosimetry can be generated based on technetium-99m images.

Most of Dr. Yang’s research is focused on ways to measure the activity of antiangiogenic agents. These agents do not typically kill tumor cells, so their activity cannot be gauged by tracking the size of the tumor. Instead, they bind to very specific angiogenic factors and interrupt their signaling pathways, slowing or halting the proliferation of new blood vessels. Drawing on this same principle, antiangiogenic agents can be radiolabeled with technetium-99m to reveal the angiogenic activity of the tumor.

Evolution of Conformal Radiation Therapy Continues **IMRT Called ‘the Next Level of Conformality’**

While researchers begin to look beyond the forms of tumors to their functional characteristics, the development of conformal radiation therapy continues. Three-dimensional conformal radiation therapy, in which the high-dose area of radiation conforms to the shape of the tumor in three dimensions, has become standard treatment for almost every type of tumor treated with radiation therapy.

“The biggest change in the past five years has been the continued evolution of conformal radiation therapy,” said James D. Cox, M.D., professor and head of the Division of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center. “The corollary to that is that we can leave out, to a better degree than ever, the normal tissues that are close by. With that, we can and have increased the doses within the tumors in many sites.”

Combining three-dimensional conformal radiation therapy with chemotherapy may allow the dose of chemotherapy to be increased as well. Gemcitabine given concurrently with three-dimensional radiation therapy

in patients with advanced non-small cell lung cancer has been shown to be better tolerated than gemcitabine plus two-dimensional radiation treatments.

According to Dr. Cox, “the next level of conformality” is intensity-modulated radiation therapy (IMRT), in which the intensity, or dose, of radiation from each direction in the three-dimensional treatment field is not uniform but is optimized to conform even more closely to the target. IMRT is especially useful in the treatment of tumors that have complex shapes.

About 1,500 patients at M. D. Anderson have undergone IMRT, primarily to treat cancers of the prostate or head and neck. “Mostly, the advances are getting to know how to use it, because we’re using it in a very high volume, day in and day out,” Dr. Cox said. “IMRT implies so many things. It implies this very strict targeting, this immobilization [of the patient], and all of these things that help us know where the tumor is.

“If you’re going to narrow the beam of radiation around the tumor, you’ve got to know all the more precisely where the tumor is.” ●

The three main angiogenesis inhibitors that Dr. Yang is studying—cyclooxygenase-2 (COX2) inhibitor, endostatin, and C225—are also promising radiosensitizing agents. Each binds to specific molecular targets: endostatin to vascular endothelial growth factor, basic fibroblast growth factor, and interleukin-8; C225 to epidermal growth factor receptor; and COX2 inhibitor to the enzyme COX2. Dr. Yang’s hypothesis is that the greater the uptake of molecular markers, measured with radiolabeled C225, endostatin, or COX2 inhibitor, the more likely a patient is to respond to these agents.

“As we develop this technique, our ability to determine whether a tumor is abnormal in a molecular way is enhanced,” Dr. Cox said. “Then, we can specifically target only the patients who have these abnormal tumors for treatment with a radiosensitizer. Right now, we’re not able to select them that way.” ●

FOR MORE INFORMATION, contact Dr. Cox at (713) 792-3411, Dr. Forster at (713) 745-4502, or Dr. Yang at (713) 794-1053.

See page 4 for related article.

Imaging Techniques Follow the Movements of Tumors During and Between Radiation Treatments

by Dawn Chalaire

Radiation treatments were once based on two-dimensional radiographic images. Then a few years ago, three-dimensional computed tomographic (CT) images came into use, giving rise to conformal radiation therapy, which has since become the standard. Now, the planning and delivery of radiation therapy are poised to move into the fourth dimension, with the advent of "real-time" imaging that follows the movements of a tumor during radiation treatment and adjusts the treatment field accordingly.

"This is more than a little bit futuristic," said James D. Cox, M.D., professor and head of the Division of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center. "But it's coming."

Current standard practice is to take CT images of the patient only once, at the beginning of the radiation treatment course, and develop a treatment plan based on those images. "And you would assume that the tumor was in the same place every day," said Dr. Cox. "Then we recognized that the tumor moves in subtle ways."

George Starkschall, Ph.D., a professor in the Department of Radiation Physics, uses the terms "intrafraction" and "interfraction" to describe the different types of tumor motion. Intrafraction motion occurs during the delivery of radiation treatment and is primarily caused by respiration. Change or displacement of the tumor from one day to the next is called interfraction motion. These changes may be caused by variations in a patient's weight or bladder and rectal volumes, as well as by changes in the size of the tumor.

To monitor tumor movement between treatments, ultrasonography is sometimes used to image prostate tumors before each fraction of radiation therapy. Protocols are also being developed to assess day-to-day changes in head and neck and spinal tumors. About a year ago, a CT scanner was installed in a radiation treatment room at M. D. Anderson—one of the first

such combinations available in the United States. An important advantage of this combined CT-linear accelerator system is that the patient remains in the same position throughout imaging and treatment. Clinical studies are investigating which patients will benefit the most from this technology.

For tumors that move during respiration, radiation physicists are attempting to calculate the treatment field and dose more explicitly. One technique is to take a CT scan at full inspiration and another one when the patient exhales. This way, the radiation physicist can identify how far the tumor actually moves during breathing and in which direction. "So we can draw a target volume that explicitly encompasses the full extent of the tumor motion during breathing," said Dr. Starkschall. "This allows us to shrink the treatment volume and spare healthy lung tissues."

Another technique that is being developed to account for the intrafraction motion of tumors is called respiratory gating. In gated treatment delivery, a device monitors the respiratory motion of the patient and, at a specified point in the respiratory cycle, triggers the linear accelerator to begin delivering radiation. At another point in the breathing cycle, radiation delivery is halted.

"This decreases the amount of motion that a tumor will undergo while the beam is on," said Dr. Starkschall. "What we're hoping to do is be able to treat a much smaller volume."

But "the ultimate goal," according to Dr. Starkschall, is real-time four-dimensional radiation therapy. With it, the delivery of radiation therapy could be modified during treatment as the position of the tumor changes, reducing the size of the treatment field even more and sparing more normal tissue.



Dr. George Starkschall, a professor in the Department of Radiation Physics, looks at computed tomographic images showing a lung tumor at full expiration and at full inspiration to determine how much the tumor moves during breathing.

"So as the tumor moves, the radiation will move with it," said Radhe Mohan, Ph.D., professor and chair of the Department of Radiation Physics. "There are all kinds of very complicating issues with that, but we think it can be done. The important thing is that to track the tumor, we have to know where the tumor is at any instant in time."

Consequently, current studies of real-time four-dimensional radiation therapy primarily involve evaluating the accuracy of imaging techniques. Kei Kitamura, M.D., a visiting scientist from Japan, is studying the use of gold seeds implanted into the tumor that can be tracked with x-rays. Dr. Starkschall is working with radiation oncologists, pulmonologists, and Dr. Kitamura to develop a protocol for this technique.

Dr. Mohan stressed that there is still much to learn about the technique before studies in patients can begin.

"If we did this four-dimensional treatment, how much gain would there be in reducing toxicity or improving control?" he said. "That's what the research is all about." ●

FOR MORE INFORMATION, contact Dr. Cox at (713) 792-3411, Dr. Starkschall at (713) 792-3292, or Dr. Mohan at (713) 745-5777.

Support Groups, Classes Teach Caregivers How to Care for Patients and Themselves

by Karen Stuyck

The scene is familiar to almost everyone who has taken care of a seriously ill loved one: A physician or nurse enters the hospital room and asks how the patient is doing; they do not, however, inquire about the caregiver's well-being.

"It's rare for a caregiver to hear, 'How are you? What are you doing to take care of yourself?'" said Laura Baynham-Fletcher, M.A., L.P.C., director of Place...of wellness at The University of Texas M. D. Anderson Cancer Center.

But that is precisely the message that caregivers need, say mental health experts. Caregivers—most often the spouse, parent, or grown child of a patient—"almost seem to need permission to do anything for themselves, someone saying, 'It's okay for you to leave this bedside and walk around the block,'" Baynham-Fletcher said. "They need to be convinced that taking care of themselves is a good thing."

Baynham-Fletcher understands the needs of caregivers better than most. As director of Place...of wellness, she oversees a wide variety of classes, programs, and support groups offered through M. D. Anderson's Integrative Medicine Program to enhance the quality of life of patients with cancer and their families and friends. She was also once a caregiver herself. For more than five years, Baynham-Fletcher cared for her husband, Cal Baynham, who died in 1996 of metastatic sarcoma. Her husband's physicians and nurse practitioners were "always asking how I was doing," Baynham-Fletcher said. "I would hope that is the case for every caregiver, but I don't think it always is."

In 1999, the journal *Cancer* published one of the first long-term scientific examinations of the mental health and quality of life of spouses or partners

caring for patients with cancer at home. The researchers found that caring for someone with cancer can take an emotional toll on the caregiver, which can lead to depression. This is especially true if the patient and caregiver have a strained relationship or a low income or are isolated.

The demands of caring for someone with cancer may cause caregivers to question the limits of their internal resources, said Phyddi Kettler, R.N., C.N.S., L.M.F.T., L.P.C., an advanced practice nurse in the Department of Neuro-Oncology's psychiatry section. "They're exhausted, and they may begin to feel incompetent and inadequate. Their distressing experiences may not be addressed because they're not the primary patient, and as a result, caregivers often feel alone in handling strong, conflicting emotions."

A common scenario, said Kettler, is a husband nearing retirement age who is suddenly faced with a cancer diagnosis. He and his wife have been looking forward to retirement and now "all of their life dreams that they have worked so hard for have been switched to fighting cancer." The wife becomes a fulltime caregiver to her husband and,

in many cases, the primary decision-maker, often a major reversal in roles. Understandably, this situation may cause "a surge of feelings, including anger, guilt, depression, anxiety, and fear," Kettler said. And frequently, the wife may feel as if she shouldn't talk about these "negative" feelings with her husband.

Kettler, who leads a supportive therapy group at Place...of wellness called "Caregivers: I've Got Feelings Too!," said many caregivers have told her, "After coming to this meeting, I know now that I'm not going crazy." In the group, caregivers discover that other people are going through similar difficulties. "From their feedback, I've learned that coming to the group strengthens them," Kettler said. Often, at the end of the meeting, members exchange phone numbers and contact each other again. "It breaks down the loneliness and isolation of the experience," she said.

Besides providing support for each other, group members might also delve into issues such as marital problems. "Pre-existing issues don't go away with cancer," Kettler said. "If anything, they

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M. D. Anderson chaplain **Sister Alice Potts**, shown here visiting with patient [REDACTED], began a weekly support group for the wives of patients with cancer 13 years ago.

Teaching Caregivers

(Continued from page 5)

may become exacerbated." In such cases, further therapy may be necessary, but discussing the problem in the group is often helpful. Finding that others face the same difficulties seems to "normalize the experience," she said. "There is a universality found among participants that I think is soothing, as well as a permission to voice both the distress and the blessings that arise during the caregiver experience."

Another support group for caregivers, called "Well Wives," was started in 1989 by Sister Alice Potts, M.A., an M. D. Anderson chaplain, after two women, both nurses whose husbands were being treated at M. D. Anderson, suggested she start a support group for the wives of patients. Sister Alice agreed and asked participants what kind of group they would like. Would they want experts to come in to talk to them? The group members decided that they were the "experts" in this situation and that they preferred to hear how other wives were dealing with their problems. Thirteen years later, the group still meets weekly at the Jesse H. Jones Rotary House, still giving participants "the freedom to say whatever is in their hearts," Sister Alice said.

Other groups are open to patients and family members, as well as to caregivers. One such group, "Families Living with Cancer," meets monthly for dinner at Place...of wellness. After dinner, smaller groups of adult patients, caregivers, teenage family members, school-age children, and even toddlers meet to share stories and offer support.

For those who can't make it to a group, the Anderson Network offers a telephone support line for caregivers and patients and an online listserv that allows caregivers to talk over the Internet with other caregivers or patients.

To participate in the support line, the caregiver phones the Anderson Network at (800) 345-6324 to request a call from another caregiver. A Network staffer then arranges the call within 48 hours. More than 700 volunteers, former patients, and caregivers answer calls for the support line. Although a caregiver might call the support line



"[Caregivers] need to be convinced that taking care of themselves is a good thing."

**— Laura Baynham-Fletcher, M.A., L.P.C.,
director, Place...of wellness**

only once, often the callers maintain a relationship by continuing to write, e-mail, or phone each other, said Laurie Albrigo, an assistant director of Volunteer Services who manages the Anderson Network.

"Talking to someone who's been through the cancer journey is vital to the caregiver," Albrigo said.

The Network's Warmnet allows caregivers and patients to share support and information about their cancer experiences online. An online listserv, Warmnet now has more than 80 subscribers who communicate with each other, Albrigo said. In addition, Warmnet holds occasional educational forums online to discuss problems such as fatigue. To subscribe, caregivers can e-mail majordomo@maillist.mdacc.tmc.edu. (Leave the subject line blank, but type "subscribe Warmnet" in the body of the message.)

In addition to emotional support, caregivers often have other needs. Several classes at M. D. Anderson address topics such as dealing with a central venous catheter (CVC) and managing the side effects of cancer treatment. Nurses in the Department

of Infusion Therapy teach the CVC class, which allows patients and caregivers to practice procedures for using a catheter. Nurses also frequently lead discussions about common treatment side effects, such as nausea, vomiting, fatigue, pain, hair loss, and lower blood cell counts, and offer advice for coping with them.

Classes and other resources for caregivers and patients are offered at Place...of wellness and in outpatient clinics and inpatient rooms. Some of the most popular classes, Baynham-Fletcher said, teach movement techniques such as yoga and tai chi, a specific skill such as art, or relaxation techniques. Caregivers also can attend an education and discussion group on end-of-life care.

Often, when Baynham-Fletcher sees caregivers and family members come to Place...of wellness for the first time, "they're checking their watches, afraid that the patient might wake up and need them. They feel they should be at the bedside 24/7." But once they come to a class, these people make connections with others in the group and hear the stories of people in similar situations. "Just taking this first step helps caregivers to become empowered to take some time to care for themselves," Baynham-Fletcher said. ●

Physicians are encouraged to refer caregivers to these available resources. Further information can be obtained from Place...of wellness at (713) 794-4700, the Anderson Network at (800) 345-6324, or online at www.mdanderson.org. A central resource for questions about all M. D. Anderson programs and services is the M. D. Anderson Information Line at (800) 392-1611.

Editor's Note: The Family and Medical Leave Act of 1993 covers employees in many work situations, allowing them to take up to 12 weeks of unpaid, job-protected leave in a 12-month period to care for an immediate family member with a serious illness. To be eligible, an employee must have worked for the employer for at least 12 months, and other restrictions apply. Details are available from the Department of Labor, listed under U.S. Government in most telephone directories.

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DiaLog

The Caregiver: An Unsung Hero

Raymond Sawaya, M.D.
Professor and Chair
Department of Neurosurgery

Facing the threat of a recurrent brain tumor that was endangering her life, a woman arrived for a second opinion, accompanied by her husband and daughter. Having battled her condition for many years, she had lost the use of her left arm and was on a downward slope that was triggered when hope began to fade. Her family's love, resourcefulness, and unwavering search for an effective remedy to her condition had led them through, among many things, an extensive search of the Internet. This was followed by calls to private foundations and societies that helped them sort through good, bad, and outright *dangerous* information (her husband's emphasis) and, ultimately, to the decision to travel across four states to come to this office.



The results of the woman's medical assessment culminated in the decision to perform an operation to remove the tumor. Despite the fears and anxieties associated with such a prospect, smiles beamed from all three faces, and the signs of relief were unmistakable. Looking at his notes and reviewing all the questions that had baffled him over the years, the husband put into words what has troubled him the most. "I have felt so responsible for leading her to the right decision," he said.

As this family exemplifies, a caregiver is a responsible protector and ally. Frequently, they are the record keepers, the translators and communicators, and the information seekers, especially when the patient is emotionally or physically handicapped. How often has the caregiver been awake all night, sat for hours in an emergency room, or battled institutional bureaucracies to obtain medical records, x-ray files, or financial clearances? These are just a few examples of the many unobserved duties that dedicated caregivers undertake.

These caregivers deserve the same compassion that is given to our patients. It can be expressed by patiently providing detailed and "jargon-free" information and by helping to lessen the caregiver's burden by referring them to specialized agencies and encouraging them to seek help, find time to rest, and engage in activities that will help them reduce stress. Our advice can be as basic and simple as encouraging them to get a good night's sleep, or we can suggest sources of help for dealing with the complex expression of emotions such as anger, helplessness, and doubt. These suggestions may seem like common sense, but they must be verbalized. Caregivers must hear these words of encouragement from physicians. If we take the time to offer help and support to caregivers, everyone benefits.

For a more detailed description of "A Caregiver's Bill of Rights," log on to http://www.mdanderson.org/Care_Centers/BrainSpinal/ and click on Brain Cancer & Treatment Information.

OncoLog

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About These Clinical Practice Guidelines

These guidelines may assist in the diagnostic evaluation and treatment of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

M. D. Anderson Cancer Center's Practice Guidelines are continually updated as new information becomes available and are being expanded to include the entire spectrum of cancer management. New guidelines for screening and diagnosis are under development. Access the most current version of all M. D. Anderson Practice Guidelines from M. D. Anderson's Home Page at <http://www.mdanderson.org>.

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CLINICAL DISCUSSION: Endometrial Cancer

Scope of This Guideline

This guideline represents M. D. Anderson's recommendations for the treatment of endometrial cancer. Diagnostic guidelines are available to assist in the evaluation of patients who have signs and symptoms suggestive of this or other gynecologic malignancies. All of these guidelines are available on the Internet via M. D. Anderson's Home Page.

The recommendations cited here are, where possible, based on data from clinical trials, and where such data do not exist or are not conclusive, they reflect a consensus of experts.

Synopsis & Highlights

Overview

Carcinoma of the uterine endometrium is the most common gynecologic malignancy. It occurs most often in postmenopausal women, and abnormal vaginal

bleeding is the most common presenting symptom. Approximately 75% of the women in whom endometrial cancer develops have a reproductive history characterized by prolonged periods of unopposed estrogen stimulation resulting from factors such as nulliparity, polycystic ovarian syndrome, use of exogenous estrogen, and the presence of estrogen-secreting tumors. These factors are therefore considered to increase the risk of this disease. Other risk factors include obesity, diabetes mellitus, hypertension, and a family history of endometrial cancer.

Approximately 97% of endometrial cancers are adenocarcinomas and begin as endometrial hyperplasia. Other types of endometrial cancer include aggressive variants, such as serous papillary and clear cell types, that develop by a mechanism different from that which causes adenocarcinomas. Malignant mixed müllerian tumor (MMMT), another variant, is sometimes categorized as a sarcoma. All of these rare subtypes are associated with poorer prognoses and require specialized treatment.

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Endometrial cancer is diagnosed by evaluation of biopsy specimens derived from endometrial curettage, which may be performed on an outpatient basis or as an intraoperative dilatation and curettage. Endometrial biopsy should be considered in all postmenopausal patients who report vaginal bleeding, in premenopausal patients who report prolonged or heavy menstrual bleeding or intermenstrual spotting, and perhaps, in certain patients who are at high risk.

Surgery is the primary treatment for endometrial cancer, and for patients at low risk for recurrence, as defined in the guideline, it is usually the definitive treatment. For patients at medium or high risk, radiotherapy (XRT) plays an important role and is administered adjuvantly as external-beam treatment, intravaginal brachytherapy, or both. XRT is employed as a primary treatment only in patients who are medically unable to undergo surgery; as a primary treatment, surgery is associated with higher survival rates. Palliative XRT is used to treat isolated advanced or recurrent tumors located in areas not previously irradiated. In cases of cervical involvement, XRT may be used prior to surgery. Chemotherapy and hormonal therapy are employed in patients with advanced disease (stage IVB, grade 2 or 3) or recurrent metastatic disease.

Initial Evaluation

Once a diagnosis of endometrial cancer has been confirmed by biopsy, the next step is to determine the extent of disease. Dr. Ramondetta recommends a computed tomographic (CT) scan if extrauterine disease is suspected or an MRI if there is concern about cervical, bladder, or rectal involvement. She also advises that consideration be given to the possibility that the malignancy is of cervical rather than endometrial origin because pathologic samples are occasionally contaminated by cervical cells during the insertion of the sampling device through the cervix. Pap tests and endocervical curettage should be part of the workup for endometrial cancer. Colon cancer also should be considered, especially in the setting of advanced disease, Dr. Ramondetta says, because the average age at presentation is similar.

Primary Treatment & Staging

The primary treatment is based on the extent of disease at presentation—as determined by clinical assessment, biopsy results, and radiographic data—and on the status of comorbid medical conditions. Prior to 1988, endometrial cancer was staged clinically; it is now staged surgically, according to the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) guidelines. Decisions about further treatment are based on the

results of surgical staging, which reflect the risk of disease recurrence and the need for adjuvant therapy.

Disease confined to the uterus

In approximately two thirds of endometrial cancers, the disease is confined to the uterus. These patients undergo total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), with intraoperative frozen section evaluation to determine the tumor grade, cell histology, and depth of myometrial invasion. Most of these patients (85%-90%) are found to have grade 1 tumors that have not penetrated more than 50% of the myometrium, placing the patient at low risk for recurrence. For patients in this category (grade 1 disease confined to stage IA, IB, or IC or grade 2 tumors confined to stage IA), no further treatment is required.

The remaining 10%-15% of patients who present with clinically confined uterine disease have adverse factors—such as tumor invasion greater than 50%, grade 2 or 3 disease, or serous, papillary, or clear cell histologies—that place them in a higher risk category. Patients who present with cervical involvement or extrauterine disease represent high-risk categories. When these factors are found intraoperatively, the surgery should include a full pelvic staging evaluation with pelvic and para-aortic lymph node sampling and biopsies

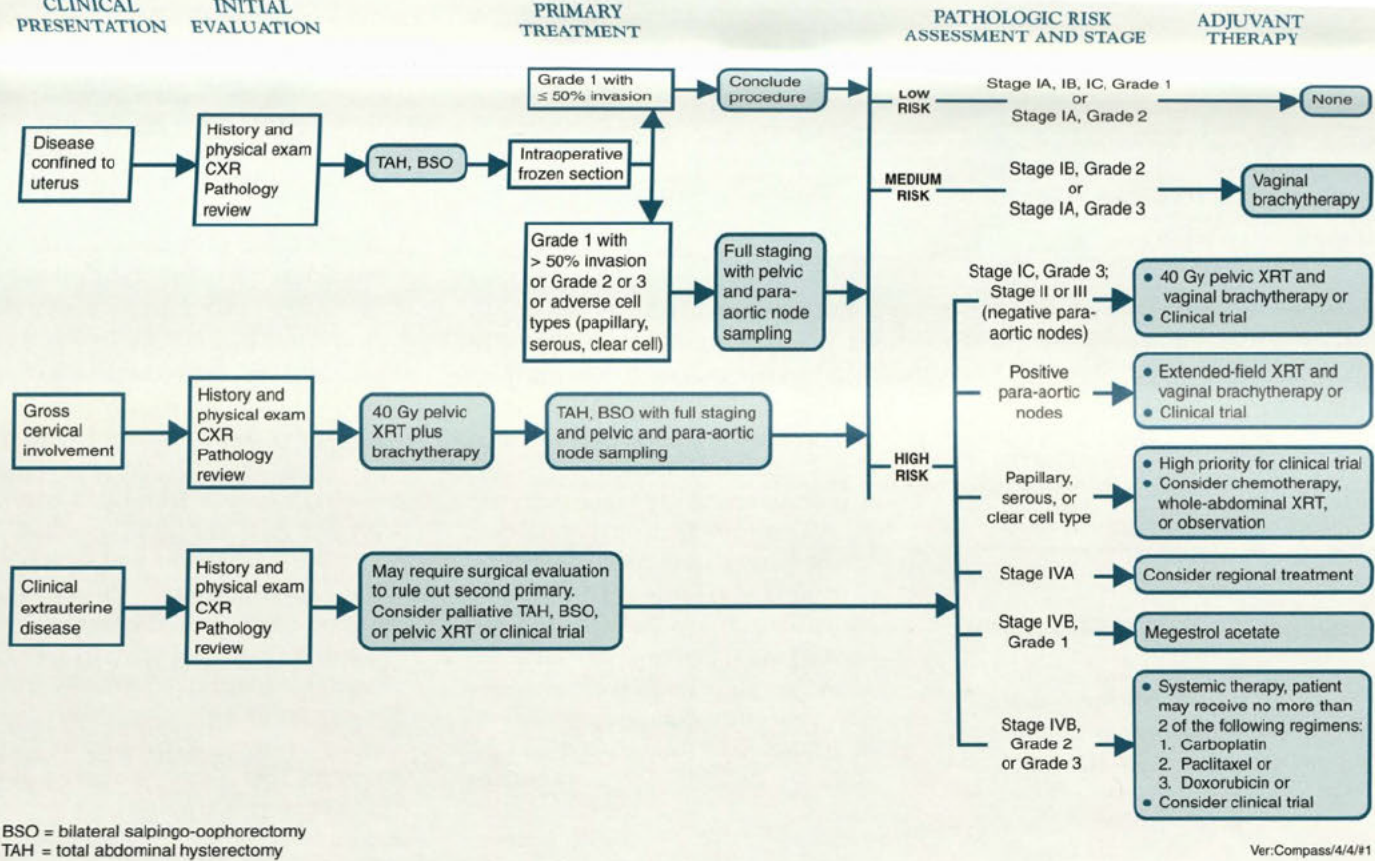
of the omentum and any grossly abnormal sites. Further biopsy and washings may be performed at the discretion of the physician.

Gross cervical involvement

When cervical involvement is evident on clinical examination, surgery should be preceded by XRT, unless it is certain that clear margins can be obtained surgically. Where there is clear cervical involvement, Dr. Jhingran recommends external-beam pelvic XRT plus abbreviated brachytherapy, with full surgical staging and TAH and BSO following in 4 to 6 weeks. "In addition to tumor reduction, radiotherapy before surgery allows us to treat the cervix and parametrium with more radiation than would be possible postoperatively because of the placement of radiation devices inside the uterus," she says. Dr. Jhingran points out that it is sometimes difficult to differentiate between uterine and cervical tumors because of their proximity to one another. In such situations, preoperative XRT can be given via cervical implant (usually for 72 hours), followed in 2 to 3 days by hysterectomy.

Clinical extrauterine disease

Patients with extrauterine disease may require surgical evaluation to determine the origin of disease (which may be a second primary tumor) and to reduce the tumor burden. "Tumor-reductive surgery is not as clearly indicated in this situation as it is in ovarian cancer, but we generally believe that maximal tumor reduction is best," says Dr. Ramondetta



Adjuvant Therapy

After primary surgical intervention and surgical staging, the need for further treatment with XRT or chemotherapy is based on pathologic assessment, depth of tumor invasion, and the presence of extrauterine disease. After surgery, patients at low risk for recurrence, as defined in the guideline, require no additional treatment. Patients with stage IB, grade 2 or stage IA, grade 3 disease are considered to be in an intermediate-risk category, for which adjuvant vaginal brachytherapy is recommended. Depending on the tumor location, grade, and depth of myometrial invasion, this may be full intravaginal brachytherapy or vaginal cuff brachytherapy, which is delivered on an outpatient basis (typically five treatments are given over 10 days) via a single line applicator that is somewhat like a plastic tampon. Available in different sizes, the applicator is inserted into the vagina, where it remains for 5 to 10 minutes, delivering a high dose of radiation directly to the vaginal cuff, which is the most common site of recurrence. "This is a very well-tolerated procedure," says Dr. Jhingran. "Virtually without side effects, it allows us to treat this area without treating surrounding tissues such as the bladder and rectum."

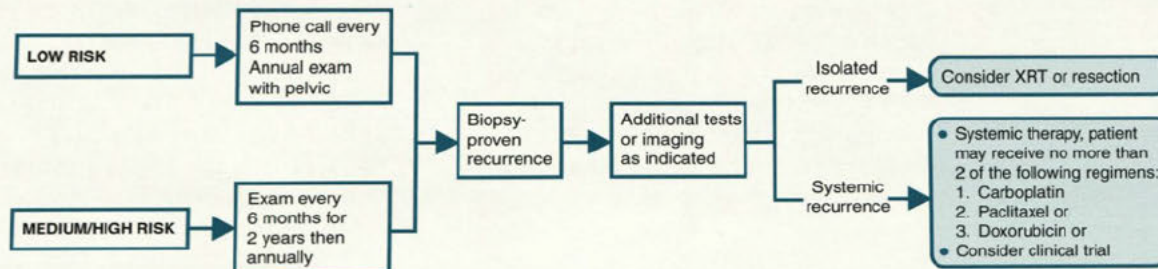
Adjuvant treatment for patients considered at high risk for recurrence should be based on specific staging parameters. For example, patients with stage IC-III disease are treated with external-beam XRT to the pelvis (or extended-field XRT if para-aortic lymph nodes are involved), followed by vaginal brachytherapy.

Endometrial Cancer (2)

 Treatment

SURVEILLANCE

TREATMENT OF RECURRENT DISEASE



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(Continued from previous page)

Papillary, serous, and clear cell or mixed cell tumors are relatively rare histologic subtypes of endometrial carcinoma that behave in aggressive ways and carry a less favorable prognosis than do adenocarcinomas. According to Dr. Burke, these rare subtypes often require systemic and combined-modality treatment, which may include chemoradiation or whole-abdominal XRT. Enrollment in clinical trials is recommended for patients with these aggressive tumors.

For patients with stage IVA disease, regional palliative treatment (surgery or XRT) may be considered. Systemic treatment is recommended for more advanced stage IV tumors; megestrol acetate is a hormonal treatment recommended for patients with stage IVB, grade 1 tumors. Stage IVB tumors of higher histologic grades may be treated with chemotherapeutic agents such as carboplatin, paclitaxel, or doxorubicin (no more than two such regimens should be used). Dr. Burke notes a resurgent interest in hormonal treatments for advanced endometrial disease, because although active chemotherapy agents produce good response rates, they are associated with short remissions. In addition, he says, many patients in this category are older, and hormonal agents are gentler and better tolerated than chemotherapy and can be taken orally. Progestogens (such as megestrol acetate) are the traditional choice for hormonal therapy because they have the longest clinical track record, but

newer agents such as RU486, third-generation aromatase inhibitors, and selective estrogen receptor modulators (SERMs) appear to be options for less toxic treatment and are the focus of clinical trials.

Surveillance

Following treatment, patients should be evaluated according to the schedule shown in the guideline. This evaluation should include the patient's history, a physical examination, and a pelvic examination. No benefit has been shown from chest x-rays, CT scans, or other more extensive evaluations in asymptomatic patients. Patients should be counseled about the symptoms they should report between regular follow-up examinations.

Recurrence

The treatment of recurrent disease is dependent upon the location, extent, and nature of the recurrence. Isolated recurrences—most often seen in the vagina—are still highly curable, especially if confined to the pelvis, and are treated definitively with surgery or XRT. Systemic recurrences may be treated with chemotherapy. Clinical trials should be considered for patients who have a recurrence of endometrial cancer. Current studies at M. D. Anderson include the use of hormonal agents and chemoradiation.

Clinical Perspectives

- *Endometrial adenocarcinoma, which accounts for most endometrial cancers, is highly curable because it causes symptoms (irregular bleeding) while still in the early stages. Our experts recommend prompt attention to patient reports of abnormal vaginal bleeding.*
- *Identification of cervical involvement and rare subtypes of endometrial tumors is important because specialized treatment is indicated. Referral or consultation with a gynecologic oncologist is recommended.*
- *The risk factors for endometrial cancer are known, and thus risk can be reduced. Weight reduction and strategies to reduce unopposed estrogen exposure are two important recommendations. For patients at high risk, enrollment in chemoprevention trials might also be considered.*

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