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REPORT TO PHYSICIANS FEBRUARY 2009 VOL. 54, NO. 2

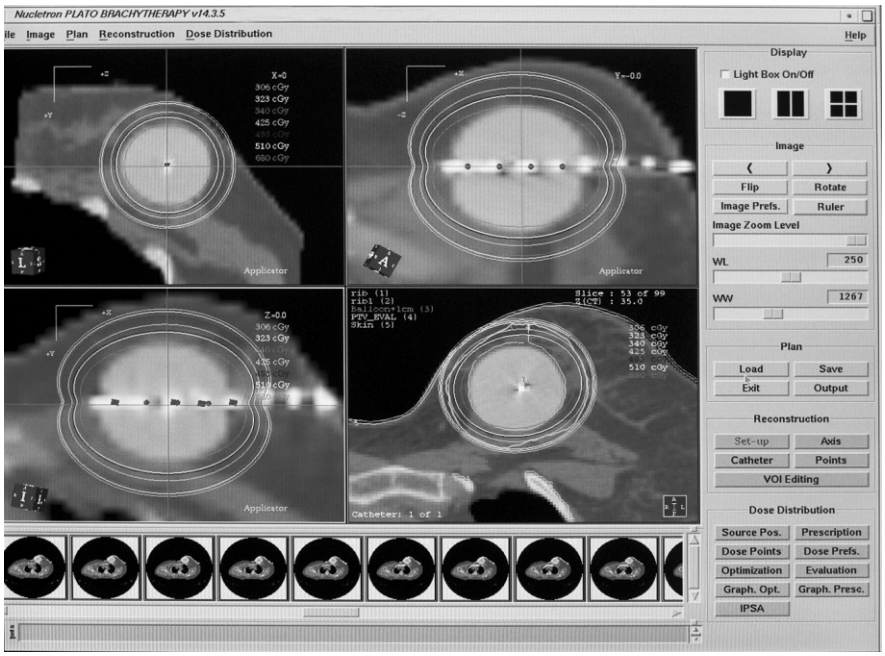
OncoLog

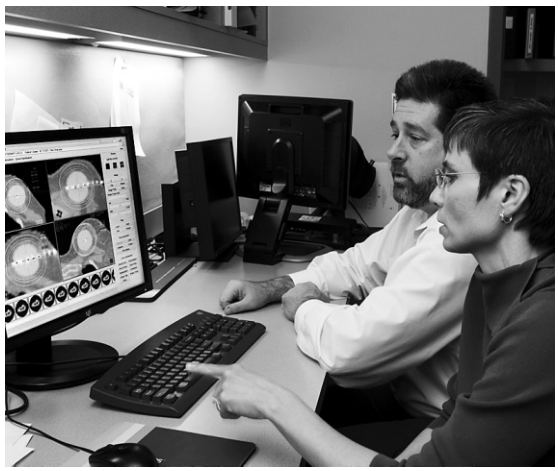
Accelerated Partial Breast Irradiation: A Promising Adjuvant to Lumpectomy

By Maude Veech

Lumpectomy offers patients with localized breast cancers a potentially curative option that spares most of their healthy breast tissue. The surgery is usually followed by adjuvant whole-breast radiation therapy for up to 6 weeks, which minimizes the risk of recurrence but increases the inconvenience and physical toll of treatment. Increasingly, however, researchers are starting to imagine a world in which selected lumpectomy patients do not have to undergo 6 weeks of radiation therapy.

Accelerated partial breast irradiation (APBI) is a relatively new therapeutic approach gaining fans among patients and (cautiously) radiation oncologists. At The University of Texas M. D. Anderson Cancer Center, APBI is performed via brachytherapy, in which the radiation source is placed using a catheter, or with radiation beams conformally shaped around the tumor bed. In addition to lasting just 5 days, APBI treatments may prove to have fewer treatment side effects. Exposing *(Continued on* **page 2***)*





Brachytherapy for breast cancer requires careful monitoring with computed tomography to ensure the catheter remains properly placed. Imaging also allows **Dr. Elizabeth Bloom** *and chief physicist* **Steve Kirsner** *to plan the radiation source's positions (seen as dots in photo above).*

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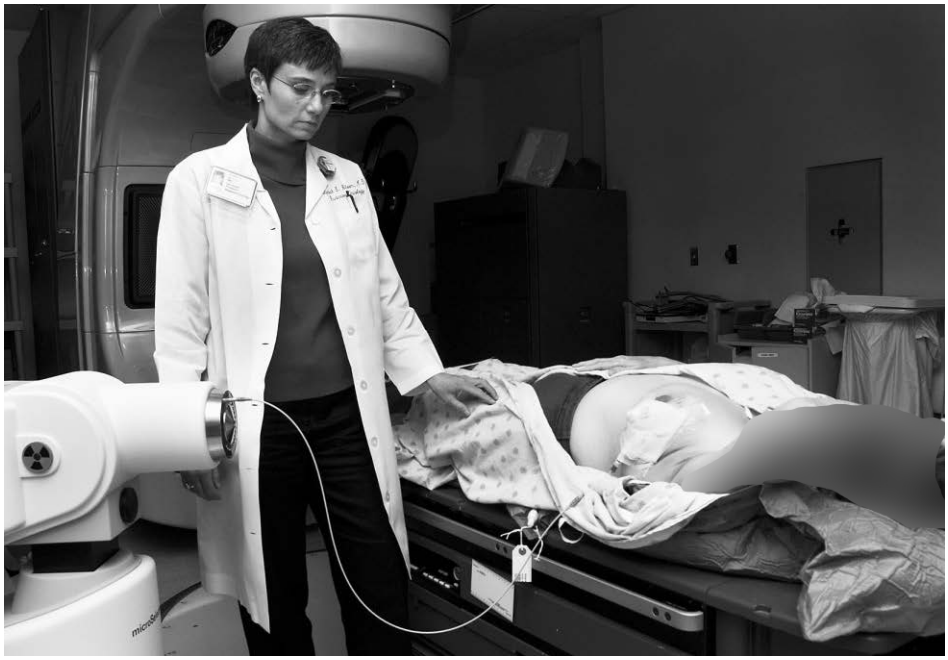
Accelerated Partial Breast Irradiation

(*Continued from* **page 1**)

less of the healthy breast, lung, and rib cage to radiation is the ultimate goal, and ongoing studies are seeking to determine if decreasing the irradiated volume does decrease the risk and severity of radiation toxicity. Still, the question remains: Does APBI brachytherapy prevent recurrence as effectively as whole-breast irradiation (WBI), which has a success rate of approximately 95%?

Elizabeth Bloom, M.D., an associate professor in the Division of Radiation Oncology, is among the M. D. Anderson oncologists trying to answer that question. She has been offering patients APBI brachytherapy at the institution's Bellaire Radiation Treatment Center since August 2008. "We show patients videos explaining both WBI and APBI, and we go through the data with them," Dr. Bloom said. "We are very up-front about the fact that no 15- to 20-year efficacy data are available for APBI, as there are for WBI." Yet, she finds many patients jump at the opportunity to try a procedure that is less lengthy than WBI and exposes them to less radiation.

"To me, it is surprising that, even though we are quite clear on the lack of long-term data compared to WBI, it does not faze them. But so far, the data look good," said Dr. Bloom, noting that APBI brachytherapy data gleaned over the past 10 years on outcomes and toxicity profiles are encouraging.



Dr. Elizabeth Bloom *checks a patient prior to MammoSite brachytherapy. The machine to the left houses a high-dose-rate iridium-192 source that travels through the cable to a catheter in the patient's breast. The position of the radiation source and the duration of treatment are controlled remotely from a computer console outside the treatment room.*

Different methods of administration

Brachytherapy requires great skill and more time of the radiation oncologist than does WBI. According to National Research Council guidelines, patients have to have brachytherapy treatments twice a day. "My office is right down the hallway from the machine," said Dr. Bloom, noting that this allows her to efficiently treat several patients with brachytherapy on any given day. Patients who wish to receive APBI at the main M. D. Anderson campus can also explore the possibility with any of the seven breast cancer radiation oncology faculty who practice there.

Though APBI brachytherapy is relatively new, the catheters used in the procedure are already in their third generation. Originally, in a procedure known as interstitial brachytherapy, multiple catheters were inserted separately to surround the tumor cavity. "This is the type of brachytherapy about which we have the most data," said Dr. Bloom. "It requires a very skilled radiation oncologist and involves 15 to 20 catheters."

However, interstitial brachytherapy for breast cancer has largely been superseded by the less-invasive MammoSite (Cytyc, Marlborough, MA), which is the method offered at M. D. Anderson's Bellaire clinic. MammoSite uses only one catheter with a collapsible balloon on the end. Once inside the breast, the balloon is expanded inside the lumpectomy cavity with a saline-contrast mixture. A central catheter within the balloon serves as a conduit for the targeted radiation source, an iridium-192 high-dose-rate seed.

Sophisticated computer planning using imaging allows specialists to define the seed positions and treatment times, which are calculated to deliver the prescribed dose to the lumpectomy cavity and margin while minimizing exposure to normal structures. Treatment is generally delivered over 5 to 10 minutes twice a day. While the balloon catheter remains in place for the duration of the treatment sessions, the iridium seed is removed from the catheter after each session.

This single-catheter technique for APBI brachytherapy does have limitations. Sometimes the balloon is too close to the skin (it needs to be at least 5 mm away) or conforms poorly to the lumpectomy cavity. Newer "hybrid" catheters (which essentially combine the single- and multiple-catheter approaches) may allow more patients to be candidates for APBI brachytherapy by addressing those limitations. "Even though we currently offer only MammoSite, hybrid catheters open even more options for APBI, and we hope to use them as indicated in the future," Dr. Bloom said.

Clinical studies available

Many of Dr. Bloom's brachytherapy patients are participating in DR08-0535, a prospective data collection study that aims to assess acute and late normal tissue sequelae in patients who

(*Continued on* **page 8**)

A New Biomarker for Bladder Cancer?

Currently, most bladder cancers can be confirmed only in later stages through invasive methods. Recent genetic research could advance the quest for reliable, noninvasive early detection.

By Joe Munch

Counting copies of the Aurora kinase A gene (*AURKA*) in exfoliated urothelial cells in voided urine may allow physicians to detect bladder cancer early, a team led by researchers at M. D. Anderson has found.

Currently available noninvasive diagnostic tests do not reliably detect low-grade bladder cancers, and various benign conditions often result in false positives on these tests, according to Bogdan Czerniak, M.D., Ph.D., a professor in the Department of Pathology and the study's senior author. While bladder cancers can be reliably detected by cystoscopy—an endoscopic procedure performed through the urethra—the procedure's invasive nature limits its use to confirming suspected cancer.

Counting the copies of *AURKA*, Dr. Czerniak said, "has the potential to be highly efficient because it actually tests for the marker that plays a major role in the development of certain key features of bladder cancer, like aneuploidy."

Aneuploidy—an abnormal number of chromosomes—is a fundamental feature of many human cancers. When the *AURKA* gene is overexpressed or amplified, as it is in many types of human cancers, it can contribute to the creation of an abnormal number of centrosomes, subsequent chromosomal missegregation, and ultimately aneuploidy during mitosis. As the level of *AURKA* rises, so does the frequency of aneuploidy.

"All bladder cancers have some degree of amplification of *AURKA*, and the degree of this amplification correlates very well with the degree of malignancy," Dr. Czerniak said.

"A fluorescence microscope and simple laboratory devices are sufficient to conduct the test, so potentially it is applicable to a wide population of patients."

– Dr. Bogdan Czerniak

In their research, which was published in the *Journal of the National Cancer Institute*, Dr. Czerniak and his colleagues first conducted a functional study to confirm that the *AURKA* gene can missegregate chromosomes in urothelial cells. They found that forced *AURKA* expression increased the number of centrosomes and the occurrence of aneuploidy in human urothelial cells. Using fluorescence in situ hybridization, the team counted the *AURKA* gene copy number in exfoliated urothelial cells in urine samples from 23 bladder cancer patients and 7 healthy controls. Using the data, the team created a bladder cancer detection model that was then tested on a separate set of urine samples from 100 bladder cancer patients and 148 controls (92 healthy individuals and 56 patients with benign urologic disorders).

According to Dr. Czerniak, the biomarker test detected bladder cancer with a high degree of specificity and reasonable sensitivity. More important, the test was able to detect bladder cancer at earlier stages than conventional methods, meaning that it could be used to identify cases that would otherwise be missed during an initial screening, leading to increased rates of bladder preservation and patient survival. The test could also be used to detect recurrences early. Additionally, said Dr. Czerniak, "It is a relatively simple test, so it can be performed in a regular hospital—a fluorescence microscope and simple laboratory devices are sufficient to conduct the test, so potentially it is applicable to a wide population of patients."

The test will not be ready for clinical application until it is approved by the U.S. Food and Drug Administration, which requires a multi-institutional validation trial. According to Dr. Czerniak, a commercial version of the test is "at least several years away." And although the test, if approved, will probably not take the place of existing diagnostic tests for bladder cancer, Dr. Czerniak said, "We know that this test can complement cytology. And there is a pretty good chance that it will expand the diagnostic armamentarium used to detect bladder cancer." ●

For more information, contact Dr. Czerniak at 713-794-1025.

Acute Lymphoblastic Leukemia:
Pediatric Regimens for Adolescents and Young Adults Yield Survival Advantages

By Don Norwood

One of the biggest successes in cancer treatment over the past 3 decades has been a drastic improvement in overall 5-year survival rates in children and middle-aged and older adults with acute lymphoblastic leukemia (ALL). In children in particular, the rates have increased from about 20% to about 80% over this time frame—encouraging news indeed for patients with ALL diagnosed at 15 years of age or younger.

The news for adolescents and young adults diagnosed with ALL is not so good, however. Unlike in children and older adults, ALL survival rates in adolescents and young adults have remained essentially unchanged since the 1970s. A treatment breakthrough for this patient group is greatly needed.

Researchers at M. D. Anderson in the Department of Leukemia and the Children's Cancer Hospital may be well on the way to such a breakthrough with their ongoing phase II study of augmented Berlin-Frankfurt-Munster (BFM) therapy. Augmented BFM is a regimen of 6-mercaptopurine, 6-thioguanine, cyclophosphamide, cytarabine, daunorubicin, dexamethasone, doxorubicin, methotrexate, polyethylene glycol-conjugated L-asparaginase, prednisone, and vincristine designed specifically for pediatric patients. In the M. D. Anderson study of augmented BFM therapy, the regimen is administered to patients 12–40 years old with Philadelphia chromosome–negative precursor B-cell or T-cell ALL or lymphoblastic lymphoma.

Dr. Michael Rytting *and other researchers at M. D. Anderson are finding success with augmented Berlin-Frankfurt-Munster therapy, a pediatric protocol for acute lymphoblastic leukemia, in adolescents and young adults.*

Thus far, the results of treatment with augmented BFM have been comparable with the promising results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a regimen designed for adults and the most common regimen for adult ALL patients at M. D. Anderson. However, augmented BFM for adolescents and young adults

with ALL has proven to be advantageous over hyper-CVAD in several areas.

"I think the success of augmented BFM is mainly due to differences in the delivery of the chemotherapy," said Deborah A. Thomas, M.D., an associate professor in the Department of Leukemia. "With hyper-CVAD, the patients get the chemotherapy in a confined period of time over 3–5 days in the hospital. The augmented BFM regimen is a sequential therapy regimen, which means that different chemotherapy agents are administered at different time points throughout a cycle."

In addition, the augmented BFM therapy is given mostly in the outpatient setting, and the regimen seems to be less myelosuppressive, so fewer transfusions are required. The medications are still given intravenously, so a central line is required, and the overall duration of therapy for the two regimens is similar.

Ongoing debate

Whether a pediatric or adult regimen should be used to treat ALL in adolescents and young adults has been an ongoing debate for several years at M. D. Anderson and other cancer research institutions around the world. Whereas M. D. Anderson researchers have found that both hyper-CVAD and pediatric regimens have been rather successful against this disease in adolescents and young adults, most studies comparing pediatric and conventional adult regimens for ALL have found the former to be much more effective in adolescents and young adults. Specifically, the results of several trials have shown that pediatric regimens produce higher survival rates in adolescent and young adult patients.

"So far, it does look like 16- to 21-year-olds do better on pediatric-type programs," said Michael E. Rytting, M.D., an associate professor in the Children's Cancer Hospital. "There are many reasons for that. ALL is a rare disease in adults, but it is the most common cancer diagnosis in pediatric patients. All pediatric hematologists and oncologists are pretty well informed and up to speed on ALL. So being familiar with the treatment regimen and disease gives us an advantage in treating adolescents and young adults."

"I think the success of augmented BFM is mainly due to differences in the delivery of the chemotherapy."

– Dr. Deborah A. Thomas

Dr. Thomas elaborated on the results of the studies comparing pediatric and adult regimens, pointing out that researchers performing a multinational trial involving ALL patients who are 16–21 years old have reported an event-free survival rate of 60%–70% for a pediatric regimen and a rate of about 40% for an adult regimen. Dr. Thomas argues that such results, which multiple studies have corroborated, mean that oncologists should choose pediatric regimens such as augmented BFM over adult regimens for ALL in adolescents and young adults. She also offers another reason why pediatric regimens are more desirable for adolescents and young adults: they are much more dose-intense (for certain nonmyelosuppressive drugs) than adult regimens are.

Physician's role

Although the augmented BFM and hyper-CVAD regimens both have been effective against ALL in adolescent and young adult patients at M. D. Anderson, a proactive approach by the patient's family physician is required for these and all other chemotherapy regimens to be effective. Dr. Rytting said that this approach includes having a healthy suspicion of leukemia, referring the patient to the proper treatment facility, and providing appropriate follow-up care.

"Newly diagnosed leukemia patients ideally should be seen at a large cancer center, where the diagnosis can be confirmed and a treatment plan put into place," said Dr. Rytting. "If they achieve remission, which requires about 4 weeks of treatment, they frequently can return to their local oncologists for the less intensive parts of their care."

Referral to large cancer centers is doubly advantageous for patients with ALL and other acute leukemias. Because patients are often quite ill when these leukemias are diagnosed, they receive rapid admittance upon referral to M. D. Anderson.

"When leukemia is suspected, patients are evaluated upon referral; there's not a waiting time," said Dr. Rytting. "They can come to the emergency room, because it is an emergency. For pediatric patients, we try to get them seen in our clinic or admitted to the hospital the day of the referral." The same process of rapid acceptance applies for adolescents, young adults, and older adults referred to the Department of Leukemia. ●

For more information, contact Dr. Thomas at 713-745-4616 or Dr. Rytting at 713-792-4855.

Gefitinib Compares Favorably to Docetaxel in Lung Cancer Trial

A large M. D. Anderson–led clinical trial of the biologic therapy gefitinib (Iressa) has shown it to be as effective as the cytotoxic chemotherapy docetaxel (Taxotere) against previously treated advanced non–small cell lung cancer. The phase III trial also showed that gefitinib, an orally administered tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), caused fewer side effects than docetaxel.

> "It's the first time that gefitinib and chemotherapy have been shown to yield a similar overall survival benefit in lung cancer."
>
> **– Dr. Edward S. Kim**

"This is the largest head-to-head trial comparing an oral biologic therapy to chemotherapy in lung cancer patients, and it's the first time that the two therapies have been shown to yield a similar overall survival benefit," said lead author Edward S. Kim, M.D., an assistant professor in the Department of Thoracic/Head & Neck Medical Oncology.

The INTEREST study was stopped early in the United States after another large study comparing gefitinib to placebo in non–small cell lung cancer showed no survival advantage. The U.S. Food and Drug Administration relabeled the drug, and it was no longer administered to new lung cancer patients. However, INTEREST continued in other countries, accruing more than 1,400 patients with locally advanced or metastatic non–small cell lung cancer that had previously been treated.

When the international INTEREST data were analyzed, the median overall survival duration for patients who received gefitinib was 7.6 months, compared to 8 months for patients who received docetaxel. The most common side effects of gefitinib therapy were rash and diarrhea, compared with the more serious low blood cell counts and infection resulting from docetaxel therapy.

Additionally, tissue samples collected from study participants were tested for mutations in the genes that control EGFR and the KRAS protein. Patients with EGFR mutations had a better response rate and progression-free survival duration with gefinitib, though overall survival was similar to chemotherapy. Patients with *KRAS* mutations did poorly on either gefinitib or chemotherapy.

Still, Dr. Kim said the finding that gefitinib yields similar overall survival with fewer side effects suggests that it should once again be considered for U.S. patients who have advanced lung cancer that has relapsed or is resistant to chemotherapy.

The study, published late last year in *The Lancet*, was funded by gefitinib manufacturer AstraZeneca. Dr. Kim has received research funding from and served as a consultant for AstraZeneca and Sanofi-Aventis, which makes docetaxel. ●

Nilotinib, Dasatinib Show Promise as Front-line Therapies for Chronic Myelogenous Leukemia

Nilotinib and dasatinib may be more effective than imatinib as front-line therapies for chronic myelogenous leukemia (CML), according to preliminary findings from two ongoing phase II trials at M. D. Anderson. While imatinib is the current standard agent for newly diagnosed CML, both nilotinib and dasatinib are approved by the U.S. Food and Drug Administration as second-line therapies.

"We are seeing more patients achieve complete cytogenetic response faster with either nilotinib or dasatinib than we did during clinical trials with imatinib," said Jorge Cortes, M.D., a professor in M. D. Anderson's Department of Leukemia and the first author of both studies. "These are early but encouraging results." A complete cytogenic response occurs when the abnormal chromosome that causes CML completely disappears.

> "We are seeing more patients achieve complete cytogenetic response faster with nilotinib or dasatinib."
>
> **– Dr. Jorge Cortes**

To date, the nilotinib and dasatinib trials have enrolled 49 and 50 patients, respectively. Nearly all patients in the nilotinib trial have had a complete response to the drug in as few as 3 months. Overall, 96% of the patients in the nilotinib trial and 98% of the patients in the dasatinib trial have achieved a complete cytogenetic response. After 1 year of therapy, 52% of the patients in the nilotinib trial and 34% of the patients in the dasatinib trial have achieved a major molecular response, a stricter measure of disease remission.

Since its approval as a front-line therapy for CML, imatinib has increased the 5-year overall survival rate for patients with the disease from 50% to 90%. While imatinib targets aberrant Bcr-Abl protein, which causes white blood cells and immature stem cells to proliferate and crowd out red blood cells and platelets, nilotinib and dasatinib target a greater range of genetic variations that lead to CML.

In each trial, doses have had to be reduced or temporarily halted for some patients because of toxicity. However, Dr. Cortes said, "Side effects so far are manageable and comparable to those seen with imatinib."

The findings were presented at the 50th annual meeting of the American Society of Hematology and published in the meeting proceedings in *Blood*. ●

Think About Your Medical Needs When Preparing for Natural Disasters

Natural disasters can strike at any time and with little warning. That's why everyone should have a "disaster survival kit" that includes an evacuation plan, emergency supplies, and important items that you want to save. If you have a serious medical condition like cancer, heart disease, or diabetes, you should have a medical-needs plan as well.

In the event of an evacuation, you may receive care from a physician who is not familiar with your condition. Without information about your medical history, that physician might have only a best guess for how to treat you. A medical-needs plan can ensure that you receive consistent care, even if it's not from your regular doctor.

Having a medical-needs plan can ensure that you receive consistent care, even if it's not from your regular doctor.

Write it down

To organize the information, create a medical information list for each member of your household. Update the information regularly and store the lists in a waterproof container in your disaster survival kit. You might also choose to save the lists in a file on your laptop computer—just remember to take it with you in an evacuation.

Start each list by recording basic information—name, address, and birthdate and the name and phone number of an emergency contact (preferably someone who lives more than 100 miles away, since it's usually easier to connect with a number that isn't in the disaster area). Follow this with the name and phone number of your pharmacy, your insurance policy number, and the name, address, and phone number of your primary physician. Attach a copy of your health insurance card.

Next, create the following sections:

- **Illnesses or Chronic Conditions.** Include your diagnosis, the date of the diagnosis, and the name of the doctor who made the diagnosis.
- **Prescription Medications.** List the dosage and how often you need to take each of your medicines.
- **Health Care Team.** Include the name, address, and phone number for each of your doctors.
- **Surgeries.** Describe every surgery you've had, including the type, the date, the hospital or clinic where it was performed, and why it was performed.
- **Food or Drug Allergies, Immunizations, Dietary Needs, Advance Directives,** and **Organ Donation Preferences,** if applicable.

Special considerations

If you are a cancer patient, the medical information list should also include your current cancer stage and the stage at the time of your diagnosis. Describe the treatments you've received, along with the dates of those treatments and the name of the hospital or clinic where you received them.

If you have a disability, it is especially important that you prepare for a natural disaster. The American Red Cross advises making a disaster emergency information list that will tell others whom to call if you are unconscious or unable to speak. Be sure the list mentions any adaptive equipment you use, such as a wheelchair or oxygen system.

Try to keep at least a 7-day supply of any essential medications on hand. It's also a good idea to talk with your pharmacist about the shelf life of your medications and ask what you should do if you don't have enough medicine after a disaster.

A little advance preparation can do a lot to keep you healthy following a natural disaster. ●

For more information, talk to your physician, or:

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

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K. Stuyck

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Accelerated Partial Breast Irradiation

(Continued from **page 2***)*

receive APBI. To qualify, patients must be at least 50 years old, have invasive ductal carcinoma or ductal carcinoma in situ, have disease-free surgical margins after lumpectomy, and have no lymph node involvement. Information is collected about long-term cosmesis and acute and late toxicities following APBI delivered via various techniques—in part to compare MammoSite with hybrid catheters. Most of the women enrolled so far have tumors that are estrogen receptor (ER) positive, which means they are more likely to be treated with hormonal therapy than chemotherapy and generally have a better prognosis.

Also available is the Radiation Therapy Oncology Group study RTOG 0413, which randomly assigns patients to receive either WBI or APBI after lumpectomy and surgical axillary evaluation. The trial is currently open to higher-risk patients (those younger than 50 years old or those who have node-positive disease or invasive breast cancer that is ER and progesterone receptor negative).

Promising data lead to further investigation

Nonrandomized, single-center studies over the past 5 to 8 years appear to have shown a low rate of in-breast cancer recurrence in lumpectomy patients after APBI brachytherapy. "A lot of women like that it is a targeted, shorter treatment with the potential for less long-term toxicity," Dr. Bloom said.

Higher-risk patients usually receive chemotherapy after a lumpectomy. "One advantage of brachytherapy is that, unlike WBI, it can be done before chemotherapy, so we don't have to delay radiation therapy 4 to 6 months for chemotherapy," added Dr. Bloom. As the randomized Radiation Therapy Oncology Group study is no longer available to low-risk patients, some patients may be offered APBI brachytherapy off-protocol. Many oncologists believe it is safe to offer APBI off-protocol to patients who meet certain criteria. The American Society of Breast Surgeons and the American Brachytherapy Society guidelines define differently those patients who can be offered APBI in lieu of WBI. "At M. D. Anderson, we are using a composite of the two societies' guidelines and being conservative," said Dr. Bloom. "One set of guidelines allows the patient to be as young as 45 years old—but we prefer the patient to be postmenopausal. We will offer APBI to treat invasive ductal carcinoma or ductal carcinoma in situ, as long as there is no lymphovascular space invasion." APBI is appropriate in such cases because the cancer is confined to a small area.

Dr. Bloom stressed the need for more data on the risks and benefits of all forms of APBI, but she finds that patients appreciate having options. "So far, APBI looks very promising for the appropriately selected patient." ●

For more information, contact Dr. Bloom at 713-745-6123.