Stereotactic body radiation therapy (SBRT), a relatively new treatment modality, has recently become a very successful treatment—and may even exceed the effectiveness of surgery—for early-stage lung cancer.

SBRT, sometimes called stereotactic ablative radiotherapy, has many similarities to conventional radiation therapy; both use multiple beams to deliver a therapeutic dose of radiation to the target tissue. However, the difference between SBRT and conventional radiation therapy is that SBRT uses more beams from many more directions, allowing doctors to administer very high radiation doses to very specific targets with less risk to the surrounding tissues.

“The key issue with SBRT is to deliver a high enough dose to ablate the tumor while sparing the surrounding tissues,” said Joe Chang, M.D., Ph.D., an associate professor in the Division of Radiation Oncology, the director of the SBRT program, and clinical service chief of thoracic radiation oncology at The University of Texas MD Anderson Cancer Center.

Planning around critical structures

Dr. Chang explained, “SBRT creates a very sharp dose gradient, which means that within 5 mm, an ablative dose drops to a safe dose. So although multiple beams hit the target, only one beam goes through the surrounding tissue at any given region.”

Because the radiation is delivered from so many angles, SBRT requires precise planning around the target area.

Dr. Joe Chang reviews a treatment plan with the 1,000th lung cancer patient to receive stereotactic body radiation therapy at MD Anderson.
This requires a 4-dimensional volumetric imaging modality, such as computed tomography (CT), that accounts for motion. These images are used to create customized treatment plans that direct several radiation beams of different intensities at different angles precisely to the tumor. Volumetric images are also taken immediately before treatment using imaging equipment attached directly to the SBRT machinery. Another option is implanting a metal fiducial marker to track the position of the tumor with x-rays.

These precise imaging methods are more important for SBRT than for conventional radiation therapy because of the higher doses SBRT can deliver to the target. Precise imaging is especially important for treating lung cancer because of the movement associated with respiration and the sensitivity of the lung and surrounding tissue to radiation. Small inaccuracies can result in large doses of radiation to healthy tissue.

**Lessons learned from 1,000 patients**

The SBRT program in MD Anderson’s Radiation Treatment Center recently treated its 1,000th patient. As more patients have been treated, physicians have been able to adjust doses and treatment plans to ensure a balance of tumor control and patient safety.

Dr. Chang said that conventional radiation therapy doses are limited to 70–80 Gy because patients cannot tolerate higher doses without significant toxicity. However, the primary advantage of SBRT is that it can deliver higher doses to the tumor because of the greater precision and number of beam angles. This difference in dosage is the key difference between conventional radiation therapy, which is limited to a local control rate of about 50%, and SBRT, which has a 98% local control rate.

Dr. Chang said, “For SBRT, we initially used a biologically effective dose of 88 Gy. As we began escalating doses,
we got improved control, but we didn’t achieve our 98% control rate until we used biologically effective doses above 100 Gy to the planning target volume.” Despite these high radiation doses, fewer than 5% of patients treated with SBRT for lung cancer experience severe toxicities to surrounding tissues when SBRT plans are well conducted.

The sensitivity of some of these surrounding tissues was unknown when SBRT was first used to treat lung cancer in 2004. For instance, the chest wall can tolerate only a certain radiation dose before patients begin experiencing severe rashes and pain. The same is true of the bronchial tree and brachial plexus, although each tissue’s dose tolerance is unique. However, these toxicities did not develop until very high doses were used, and they could typically be addressed by adjusting treatment plans.

The other major adjustment that had to be made was the assessment method used after treatment. Although up to 20% of post-SBRT CT studies show worsening consolidation—which sometimes indicates local recurrence—positron emission tomography (PET) and biopsies done to confirm these findings are often negative. Dr. Chang and his colleagues have found PET to be much more accurate for post-SBRT assessment than CT, but only beginning 6 months after treatment. By comparison, the effectiveness of conventional radiation therapy can be assessed by PET 3 months after treatment.

Finally, and perhaps most importantly, the physicians in the Radiation Treatment Center have found that SBRT can be used to treat patients with recurrent lung cancer—including some previously treated with conventional radiation therapy—or other cancers that have metastasized to the lung. Many of these cancers were previously believed incurable, but SBRT shows the same local control rate of 98%, and some of these patients are even cured of their cancers. Chang and his colleagues have developed a model to predict the toxicity of SBRT in patients who were previously treated with radiation therapy.

**Trends in SBRT**

National hospital surveys have shown a sizable leap in SBRT usage in recent years. Similarly, MD Anderson’s SBRT numbers have increased substantially. In 2004, when the hospital first acquired the equipment, it was used to treat only about 30 patients. Now, the Radiation Treatment Center treats nearly 240 patients a year using SBRT. This number may further increase because of the Lung Cancer Screening Program, which was launched in the summer of 2011.

Because of the success of SBRT for lung cancer, there are proposals that it can be considered a cure for early-stage lung cancer. Previously, the only known cure for such cancer was surgical resection, which can cause significant surgical complications and remove vital tissue from the lung itself.

Because of its success against lung cancer, SBRT also has been studied as a treatment for other cancers, including those of the liver, spine, and pancreas. Many cancer types metastasize to the lung, and there are initial results showing that SBRT can improve local control of these metastases. However, it is not yet known whether this local control can improve survival rates. Dr. Chang and others are currently investigating this possibility.

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**A Patient’s Perspective**

The 1,000th patient to receive stereotactic body radiation therapy (SBRT) for lung cancer at MD Anderson’s Radiation Treatment Center, described her experience at her first treatment session. “First, I came in for some preliminary scans, then I came in last week for some treatment planning CT scans, and now I’m here for my first treatment,” she said. These scans were used to design her treatment plan and construct a custom treatment couch.

“Dr. Chang told me that I only need four treatments,” said. “The doctors and nurses were very good about explaining everything; they’re really thorough and very nice, and they made sure I understood the schedule and plan before I was treated.” SBRT is a complex procedure that uses advanced equipment, and it is critical that the patient understands his or her own treatment protocol and the possible risks and benefits of it.

said that she was confident and calm during her treatment because it was clear that all of the staff treating her understood and could clearly explain what was happening.

advises other lung cancer patients to seek treatment at a large cancer center with an experienced staff. She also advises anyone who smokes to quit, no matter how hard it is, because the alternative may be lung cancer. She is proud to have convinced her two granddaughters to stop smoking.

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**FOR MORE INFORMATION**

- Call the Thoracic Care Center at 713-792-6110
- Visit www.mdanderson.org/radiationtreatmentcenter
Inflammatory Breast Cancer: Clinical Challenge, Research Enigma

By Sunita Patterson

Inflammatory breast cancer (IBC) stands apart from other cancers of the breast in its unusual clinical presentation, its aggressiveness, and its poor prognosis. Researchers and clinicians are working to clarify what distinguishes IBC from other breast cancers and to discover treatments that improve patient outcomes.

Although IBC accounts for only 2%–5% of breast cancers, it is responsible for 8%–10% of breast cancer-related deaths. “IBC has a strong tendency to metastasize. In fact, a third of patients have metastases at diagnosis,” said Naoto T. Ueno, M.D., Ph.D., a professor in the Department of Breast Medical Oncology and executive director of the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic at The University of Texas MD Anderson Cancer Center. The IBC program at MD Anderson was the first clinic in the world devoted to IBC and is the largest today, treating about 100 patients each year.

Symptoms and diagnosis

Because IBC is rare and its symptoms differ from those of more typical breast cancers, misdiagnosis and less-than-optimal treatment are common, both of which diminish survival outcomes.

The first challenge that IBC presents clinicians is that it does not look like a typical breast cancer. It often appears to be and is misdiagnosed as an infection or a rash. The primary symptoms are usually rapid breast enlargement and erythema covering most of the breast; there may not be any lump.

For most patients with breast irritation and redness, mastitis is the problem, and an antibiotic will help. However, according to Dr. Ueno, if there is no response to the antibiotic in 1–2 weeks and the breast remains red, the physician should suspect IBC and order a biopsy right away. “We don’t want to waste a lot of time with this disease,” Dr. Ueno said, “because it increases the chance of metastasis.”

Both a core needle biopsy and a punch biopsy of the skin should be done. When there is no clearly defined mass, Dr. Ueno recommends directing the needle where the most swelling and redness exist. In patients with IBC, the skin specimen will often show extensive dermal lymphatic invasion. However, in the presence of persistent symptoms, negative biopsies do not rule out cancer completely.

Along with the biopsies, the patient should undergo mammography. If the results are negative, magnetic resonance imaging and ultrasonography should be considered.

Treatment

“Many community physicians will just see one case of IBC in their entire practice,” Dr. Ueno said. For this reason, he strongly recommends that patients with IBC be referred to a clinic specializing in IBC treatment. “These patients need a specific workup and a multidisciplinary care team,” he said.

The MD Anderson IBC clinic usually sees patients within 48 hours of their referral or self-referral. Typically, patients initially come to MD Anderson for 10–14 days of testing and meeting with medical, surgical, and radiation oncologists. The workup consists of repeat breast imaging (mammography, magnetic resonance imaging, and ultrasonography), remapping of the lymph nodes, blood tests, a pathologic review, and sometimes a positron emission tomography–computed tomography scan or a computed tomography scan with a bone scan.

Treatment of nonmetastatic IBC differs from that of other breast cancers in that systemic therapy is given preoperatively to debulk the disease as much as possible. Surgery and radiation therapy follow. Because treatment usually begins with chemotherapy, a medical oncologist is usually consulted first. But Dr. Ueno recommends that surgical and radiation oncologists with expertise in IBC also be involved from the beginning. “The optimal extent of local treatment can be difficult to judge when there isn’t a clear mass and the redness is diffuse,” he said, adding that coordinated care by an experienced team can reduce the possibility of errors.

The typical treatment course takes 6 months. The standard chemotherapy regimen involves treatment with paclitaxel and the combination of 5-fluorouracil, either doxorubicin or epirubicin, and cyclophosphamide over a period of 24 weeks. Patients with HER2-positive disease also receive trastuzumab. Many patients can receive chemotherapy in their own communities and return to Houston every 6 weeks for evaluation. “Our patients come from all over the country, and some aren’t able to stay in Houston for 6 months,” Dr. Ueno said. “But we highly recommend that our patients receive their surgery and radiation therapy at MD Anderson.” Patients who are eligible for a clinical trial are encouraged to receive all their treatment at MD Anderson.

Patients whose IBC responds to chemotherapy typically undergo mastectomy with complete axillary lymph node dissection. Patients whose disease does not respond to chemotherapy, particularly if negative surgical margins are unlikely to be achieved, are not good candidates for surgery. These patients may undergo additional chemotherapy...
and/or radiation therapy and later be reevaluated for surgery.

Radiation therapy for IBC targets the chest wall and the lymph nodes in the axillary, infraclavicular, supraclavicular, and internal mammary regions with a combination of electron and photon tangent fields or matched electron fields to minimize the risk to nearby organs. Treatment doses and schedules vary among institutions, but at MD Anderson, an aggressive twice-daily schedule and a total dose of up to 66 Gy are preferred. Radiation therapy may last 5–8 weeks.

A final component of treatment for patients with hormone receptor-positive disease is endocrine therapy for 5 years, beginning after surgery.

Follow-up is recommended at intervals of every 3 months for 2 years after the completion of radiation therapy, then every 6 months for 2–3 years, and then once a year. The follow-up appointment consists of symptom evaluation, a physical exam, and basic blood tests. “We’ve cut back on imaging during follow-up visits,” Dr. Ueno said. “It hasn’t proven to improve long-term outcomes.” Of course, if symptoms are suggestive of metastasis, a full workup, including imaging studies, is done.

The best outcome is seen in patients who have a pathologic complete response in the surgical specimen. “Unfortunately,” Dr. Ueno said, “most patients have some extent of residual disease.” Although the addition of neoadjuvant systemic therapy has improved the survival rate significantly, it is still only 30%–40% at 5 years.

Aside from the availability of coordinated multidisciplinary care, another advantage of patients’ being treated at a comprehensive cancer center is the access to clinical trials. Because of the low survival rates for IBC patients, Dr. Ueno recommends considering initial treatment in a clinical trial. “Of course, a trial is always experimental,” he said. “But a standard treatment that’s not fully effective is also not the ideal treatment.”

**Researching causes and cures**

Discovering better treatment strategies is a driving force behind the research component of MD Anderson’s IBC program. “There are three research questions we’re trying to answer,” Dr. Ueno said. “What are the differences between IBC and other breast cancers? Can we identify an IBC-specific target for targeted therapy? What are the molecular risk factors for developing IBC?”

Currently, IBC is a clinical diagnosis based on the patient’s symptoms; pathologic results consistent with IBC are not a requirement for the diagnosis. To identify molecular differences between IBC and noninflammatory breast cancers, Dr. Ueno’s research group has been looking at differences between the DNA, RNA, and protein levels in IBC and noninflammatory breast cancer specimens.

“So far, there hasn’t been a clear-cut difference in tumor mRNA levels between IBC and other breast cancers,” Dr. Ueno said. This raises the question: Is IBC a distinct entity that has an aggressive, metastatic phenotype, or are IBC and noninflammatory breast cancer the same biological entity that can grow either rapidly and aggressively or more slowly?

One challenge in the past was that the rarity of IBC made it difficult to obtain enough specimens for meaningful analyses. This need prompted the formation of an IBC registry at MD Anderson in 2006. The registry collects tumor, blood, and skin specimens from around the world, along with epidemiological data. The collection of specimens and data led to the definition of universal diagnostic criteria for IBC by participating institutions in 2008.

Forty samples from the registry are now being submitted to the International Cancer Genome Consortium for whole-genome sequencing. Dr. Ueno is hopeful that the information gained will suggest appropriate targets for treatment.

**Possible treatment targets**

As in other cancers, one avidly investigated treatment strategy involves targeting genes or proteins that are highly expressed in tumor cells with an agent that inhibits that gene or protein and thereby blocks tumorigenesis or metastasis. One such target that Dr.
Inflammatory Breast Cancer

[Continued from page 5]

Ueno’s group is investigating epidermal growth factor receptor (EGFR). In an MD Anderson study, EGFR was found to be overexpressed in 30% of IBC tissue specimens, and EGFR overexpression was associated with poor prognosis. Preclinical studies demonstrated that EGFR inhibition was a promising anti-IBC strategy. This work has advanced to a phase II clinical trial of the EGFR-targeting antibody panitumumab in patients with IBC. Other MD Anderson clinical trials are testing the targeting of histone deacetylase with the inhibitor entinostat and the targeting of fibroblast growth factor receptor 3 and vascular endothelial growth factor receptor with the inhibitor dovitinib.

An alternative hypothesis is being pursued by a team of researchers led by James Reuben, Ph.D., a professor in the Department of Hematopathology, and Wendy Woodward, M.D., Ph.D., an associate professor in the Department of Radiation Oncology. These investigators, with Dr. Ueno, are looking at whether the lethal potential of IBC lies not in the tumor cells themselves but in the microenvironment. It may be that immune system or inflammatory factors present in some patients induce tumor cells to act more aggressively.

This line of research has led to investigation of cyclooxygenase 2 (COX2), an enzyme associated with inflammation. The group, with Peiyi Yang, Ph.D., an assistant professor in the Department of General Oncology, tested fish oil, which acts as a COX2 inhibitor, in vitro and saw a reduction in both the proliferation of IBC cells and the formation of mammospheres, an indicator of the presence of cancer stem cells. “Fish oil doesn’t have a lot of side effects, so we’re trying to develop this as a clinical trial,” Dr. Ueno said.

Statins are another avenue of exploration. This class of drugs, commonly used for patients with high cholesterol or triglyceride levels, is also thought to modulate inflammation. “If inflammation is a clinically relevant target, statins or COX2 inhibitors or fish oil could be a future therapy,” Dr. Ueno said. “It’s a matter of determining which pathway is best to target.” He anticipates a clinical trial in 1–2 years.

The IBC research group has been testing a new strategy for phase I clinical trials. An experimental drug is given to patients who previously received standard therapy and still have circulating tumor cells, or micrometastases, in the blood or bone marrow. A test for measuring these cells was developed by Dr. Reuben. The researchers hypothesize that the persistence of circulating tumor cells after treatment for IBC identifies patients at higher risk of recurrence or metastasis. If a drug eradicates those cells, it may be successful in preventing recurrence, and thus a larger trial with traditional disease outcome measures would be warranted.

Potential impact

Dr. Ueno is passionate about the need to study IBC even though it’s “rare.” “People keep asking, why are we investing so much effort in an ‘orphan’ disease?” he said. “It’s true that IBC is rare in terms of incidence. But from the mortality perspective, IBC isn’t rare. It’s a killer.”

FOR MORE INFORMATION

Dr. Naoto Ueno..................713-792-8754

ADDITIONAL RESOURCES


The MD Anderson IBC program hosts a Web page, Facebook page, and Twitter account with research updates and patient information:
• www.mdanderson.org/IBCProgram
• www.facebook.com/InflammatoryBreastCancer
• twitter.com/InflammatoryBCa

Dr. Ueno posts information for patients, clinicians, and researchers on Facebook and Twitter:
• www.facebook.com/ntueno
• www.twitter.com/teamoncology

CLINICAL TRIALS: Inflammatory Breast Cancer

Phase II of panitumumab, nab-paclitaxel, and carboplatin for patients with primary inflammatory breast cancer (IBC) without HER2 overexpression (2008-0372). Principal Investigator (PI): Naoto Ueno, M.D., Ph.D. This trial will study the effectiveness of the combination of two neoadjuvant chemotherapy regimens—panitumumab, nab-paclitaxel, and carboplatin plus 5-fluorouracil, epirubicin, and cyclophosphamide—in the treatment of IBC.

Phase I/II of entinostat and lapatinib in patients with HER2-positive metastatic breast cancer in whom trastuzumab has failed (2010-0842). PI: Dr. Ueno. The main goal of this study is to find the highest tolerable doses of entinostat and lapatinib that can be given in combination to patients with advanced or metastatic breast cancer (including an IBC cohort). The effectiveness of the combination will also be studied.

A phase II study of TKI258 (dovitinib lactate) as salvage therapy in patients with first local or distant relapse (2010-0296). PI: Ricardo Alvarez, M.D. This study’s objective is to determine the overall response to dovitinib in patients with local or distant relapse of HER2-normal, metastatic IBC.

A phase II study of preoperative capecitabine and concomitant radiation in women with advanced inflammatory or non-inflammatory breast cancer (2009-0087). PI: Wendy Woodward, M.D., Ph.D. The goal of this study is to find out whether capecitabine and radiation therapy can help to control breast cancer that did not respond well to chemotherapy.

FOR MORE INFORMATION
Reducing Cancer-Causing Chemicals in Outdoor Cooking

Tips for healthy grilling

How you cook your meat could be increasing your risk of cancer, but making a few simple changes can yield major health benefits.

While adequate cooking is necessary to kill harmful germs in meat, research has shown that cooking meat at very high temperatures creates potentially dangerous chemicals. Grilling any type of meat, even chicken or fish, until it’s charred—partly blackened—can add to your risk of cancer, according to the American Institute for Cancer Research.

A University of Minnesota study found that regularly eating charred, well-done meat may increase a person’s risk of pancreatic cancer by up to 60%. Other research suggests that eating a lot of well-done and barbecued meat might increase the risk of colorectal and breast cancers.

When muscle meats such as beef, pork, lamb, fish, and poultry are cooked, cancer-causing chemicals called heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) may be formed. HCAs are created by the burning of amino acids and other substances in meat cooked at very high temperatures. PAHs are produced when fat and juices from meat grilled directly over an open fire drip onto the fire, causing flames and smoke.

What can you do to decrease the amount of these chemicals in your food?

Precook before grilling. You can reduce the time on the grill—and the HCAs produced—by first partially cooking meat or poultry indoors for 2–5 minutes in the microwave or oven at low heat. This prevents the formation of some of the potentially harmful chemicals while keeping the food moist. Then finish up the meat on the grill.

Season and marinate your food. Use garlic, rosemary, and sage, which are antioxidant seasonings that can decrease the formation of HCAs and PAHs. Cook with virgin olive oil, which also has antioxidant properties. Marinating grilled foods also makes them taste better.

Limit your meat intake. Diets high in red meat, such as beef, pork, and lamb—and especially processed meats, such as hot dogs, bacon, ham, cold cuts, and sausage— increase colorectal cancer risk, according to the American Institute for Cancer Research. The institute suggests limiting your consumption of red meat to 18 ounces per week.

Grill fish instead. Fish contains less fat than do red meat and poultry, making it less likely to create PAH-carrying smoke. Since fish requires less cooking time on the grill, exposure to carcinogens is also reduced.

Prepare your grill. Scrub your grill thoroughly after each use. Before using it the next time, lightly oil your grill to keep charred material from sticking to the food, or spread aluminum foil on the grill. Poke small holes in the foil to allow fat to drain.

Eat more fruits and vegetables. Research has shown that diets high in plant foods can lower your chances of developing several types of cancer. At your next cookout, try grilling some fruits and vegetables, which may not create carcinogens. You’ll get more nutrients if you don’t peel the vegetables before grilling. Use a light brushing of canola or olive oil on the vegetables and fruits to help prevent sticking to the grill.

You can also add fruit to the meat. Researchers at Michigan State University found that adding cherries, a great source of antioxidants, to ground beef prior to pan frying reduced the HCAs by about 70%. The researchers suggested mixing a cup of chopped tart cherries with a pound of ground beef.

Turn down the heat. Meat cooked at temperatures above 300°F produces more HCAs. Well-done, grilled, or barbecued chicken and steak, for instance, all have high concentrations of HCAs. When grilling meat, lower the settings on gas grills. On charcoal grills, increase the distance between the food and the hot coals by spreading the coals thin or propping the grill rack on bricks. Charcoal briquettes and hardwoods, such as hickory and maple, burn at lower temperatures than softwoods such as pine.

Try other cooking methods. Cooking your meat by braising, steaming, poaching, stewing, roasting, or microwaving produces fewer of the harmful chemicals than does grilling. These methods might not qualify as outdoor cooking, but it’s a short walk from the kitchen to the backyard.

These tips should make your next backyard barbecue healthier.

— K. Stuyck

FOR MORE INFORMATION
- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
Online Program Fosters Effective Physician–Patient Communication

By Natalie Freed

A new series of continuing medical education (CME) courses is available to help health care providers develop the communication skills they need.

“Effective communication is no longer a luxury in health care,” said Walter Baile, M.D., a professor in the Departments of Psychiatry and Behavioral Science at The University of Texas MD Anderson Cancer Center. “Communication skills are a key factor in determining patient satisfaction, quality of care, and health outcomes.”


The success of the course led the Department of Faculty Development to recruit Dr. Baile as the program director for an innovative series of CME communication courses, the Program for Interpersonal Communication And Relationship Enhancement (1*Care), which began in 2006 as a series of lectures and interactive workshops derived from techniques of psycho- and sociodrama.

An interactive Web site, www.mdanderson.org/icare, was launched in 2009. Now considered the cornerstone of the program, the site averages 7,000 visitors per month. 1*Care offers a library of information to support patients, caregivers, and children in addition to courses teaching practical communication skills for physicians. These online courses are convenient and accessible to a vast audience, requiring no payment, membership, login information, specific schedules, or long-term commitments. CME credit is available for physicians who desire it.

“We educate a broad range of people, including physicians, nurses, and fellows at MD Anderson and other institutions worldwide,” said Cathy Kirkwood, M.P.H., the project director of 1*Care.

The online 1*Care content for physicians is separated into modules of fundamental communication skills and more specific communication skills such as assessing nonverbal communication, breaking bad news, discussing medical errors, effectively acknowledging emotions, determining the informational and emotional needs of a patient, and developing collaborative relationships with patients and coworkers.

“It also includes material on how to teach communication, interviews with patients and families about effective communication, and videos on the challenges of being an oncologist,” said Ms. Kirkwood. The videos are accessible through iTunes U and are easily adaptable for use in teaching environments.

FOR MORE INFORMATION
- Visit www.mdanderson.org/icare
- Call or email Cathy Kirkwood, M.P.H., at 713-745-3138, cdkirckwood@mdanderson.org

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