

Specialized Care Improves Lives of Patients With Head and Neck Lymphedema

By Bryan Tutt

A unique program is producing dramatic results for patients with head and neck lymphedema, a side effect of cancer treatment that can interfere with a patient's ability to speak, swallow, or breathe.

Lymphedema is generally not painful but can be disfiguring, and no cure is available. In cancer patients, lymphedema is usually caused by lymph node damage or scarring of lymphatic vessels following surgery or radiation therapy. "Any treatment that impairs the lymphatic drainage system can result in lymphedema," said Jan S. Lewin, Ph.D., a professor in the Department of Head and Neck Surgery and chief of the Section of Speech Pathology and Audiology at The University of Texas MD Anderson Cancer Center.

A patient is shown at a baseline evaluation for lymphedema of the neck 7 weeks after the completion of chemoradiation for cancer of the mouth (left) and after 10 months of lymphedema therapy (right).



Lymphedema is commonly seen in the arms of patients treated for breast cancer or the legs of patients treated for genitourinary cancers. Lymphedema in the head and neck region is much less common than lymphedema in the extremities, and it presents different challenges for patients and clinicians.

The effects of head and neck lymphedema are not simply cosmetic. When lymphedema affects the lips, tongue, eyes, or throat, the functional problems can be severe and even life-threatening. Swelling of the face, mouth, and neck can substantially impede speaking and swallowing. Swelling around the eyes may affect reading, writing, and even walking. Lymphedema that affects the airway may result in diffi-

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Specialized Care for Head and Neck Lymphedema

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culty breathing. The emotional consequences—frustration, embarrassment, and even depression—can also be significant.

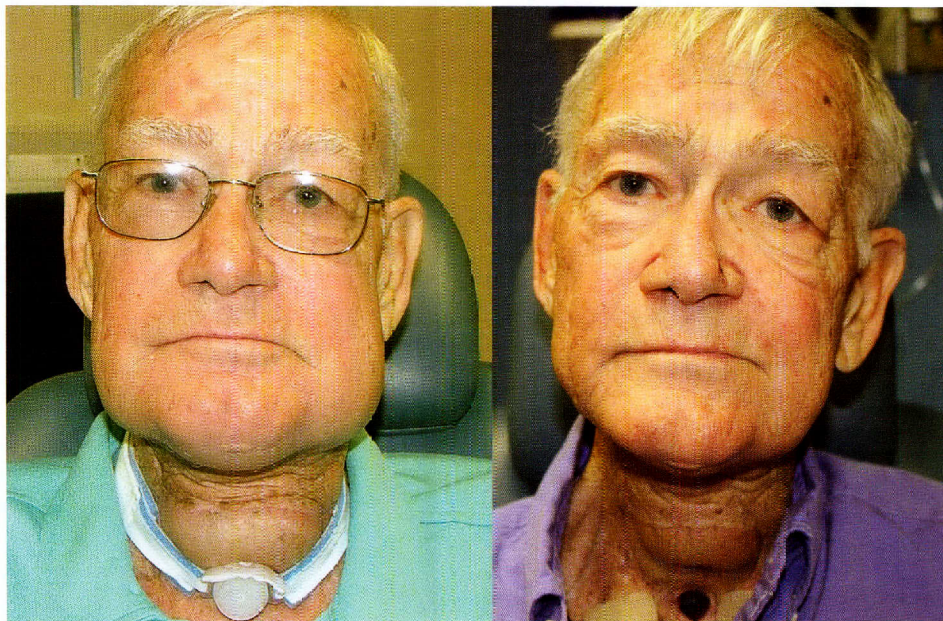
Lymphedema management

Complete decongestive therapy is the gold standard for the treatment of lymphedema. Its goal is to move lymphatic fluid away from congested areas through unimpaired pathways. This therapy combines manual lymph drainage, which uses gentle massage to facilitate fluid movement; compression therapy, which keeps the fluid from re-filling the congested area; targeted exercises to maintain tissue elasticity; and skin care to prevent infection.

Although lymphedema is most often managed by physical, occupational, or massage therapists with specialized training, many of these certified lymphedema therapists will never see a patient with head and neck lymphedema.

“Extremity lymphedema is the physical or occupational therapists’ area of expertise. When lymphedema occurs in the head and neck region, it often affects the ability to speak, swallow, or breathe, and its treatment requires a unique skill set,” Dr. Lewin said. She believed that head and neck lymphedema treatment outcomes could be improved by training speech pathologists—who were already familiar with the anatomy and physiology of the head and neck and were likely to be treating the patients for speech and swallowing dysfunction—to become certified lymphedema therapists.

The head and neck lymphedema program in the Department of Head and Neck Surgery began in 2006 and



A patient is shown at a baseline lymphedema evaluation 6 weeks after surgery to remove cancer of the larynx (left) and after 5 months of lymphedema therapy (right).

now has two speech pathologists who are certified lymphedema therapists, Brad Smith and Leila Little. They provide evaluation and treatment to patients referred by MD Anderson physicians or by physicians outside the institution as well as patients who are self-referred but have been diagnosed with head or neck lymphedema by a physician.

The program of management for head and neck lymphedema at MD Anderson consists of outpatient treatment provided by a certified lymphedema therapist combined with a self-directed treatment program that the patient can perform at home. Although some patients come for routine outpatient visits, most can manage their lym-

phedema at home after one to three visits and return in 4–6 weeks for a follow-up evaluation. “The ability to easily access the head and neck region allows much of the therapy to be performed at home, a feature that enhances patient adherence to the therapy regimen,” Mr. Smith said.

During their initial visit, in addition to receiving manual lymph drainage, most patients are provided with compression garments to maximize drainage from swollen areas (see photo, right). Although some patients require custom-made garments, such garments are often expensive and not always covered by insurance. Ms. Little said that less expensive standard compression garments can usually be modified to fit patients. She added that these customized garments are comfortable and can be worn while sleeping if needed.

Long-term improvements

“The majority of our patients tell us that their swelling is worst when they first get up in the morning and improves throughout the day. That’s the opposite of what patients with

“When lymphedema occurs in the head and neck region, it often affects the ability to speak, swallow, or breathe, and its treatment requires a unique skill set.”

– Dr. Jan Lewin



A patient who had been previously treated for cancer in multiple sites on the head and neck is shown at a baseline lymphedema evaluation 6 weeks after hemimandibulectomy (left) and after 6 months of lymphedema therapy (right).



Compression garments, which help maximize lymph drainage, are an integral part of complete decongestive therapy for most patients with head or neck lymphedema.

extremity lymphedema experience; their swelling increases throughout the day," Mr. Smith said. "This is why management of swelling in the arms or legs is often a life-long process. In contrast, patients with head and neck lymphedema often respond quickly and avoid the

need for lifetime treatment."

According to Dr. Lewin, there is no standard objective measurement to evaluate treatment outcomes in patients with lymphedema in the head and neck area. Instead, photography and tape measures are used to document change over the course of treatment. "Our data over the past 6 years show that more than half of patients demonstrate improvement on their first follow-up visit, and more than 70% show an overall reduction in lymphedema if the patient has been compliant with the treatment program—regardless of whether the setting is outpatient or home-based," she said.

Mr. Smith said, "We can almost eliminate the swelling in patients with mild edema within 6 months. For patients with severe scarring and more swelling, it may take longer. Even if we can't eliminate the swelling, we're almost always able to get some improvement."

Although the management of lymphedema should first be attempted with complete decongestive therapy, Dr. Lewin said that surgery is an option

"Our data over the past 6 years show that more than half of patients demonstrate improvement on their first follow-up visit."

– Dr. Jan Lewin

for patients with chronic, severe head or neck lymphedema when standard methods of treatment are ineffective.

Ms. Little added that better long-term results are achieved when lymphedema is treated in its early stages—before the tissue becomes fibrotic. Therefore, patients whose edema has not resolved within 4–6 weeks of the completion of treatment for head and neck cancer should be referred for evaluation. "There are usually treatment options available," she said. "Lymphedema isn't something a patient should have to live with." ■

FOR MORE INFORMATION

Dr. Jan S. Lewin.....713-745-2309

ADDITIONAL RESOURCES

Smith BG, Lewin JS. Lymphedema management in head and neck cancer. *Curr Opin Otolaryngol Head Neck Surg.* 2010;18:153–158.

The University of Texas MD Anderson Cancer Center. *Lymphedema specialists tackle post-surgery swelling* [video]. 2013. www3.mdanderson.org/streams/CompactVideoPlayer2.cfm?xml=cfg/Lymphedema-Post-surgery-Swelling

Targeted Cancer Therapies May Help Ov

By Sarah Bronson

Some cancer cells are resilient enough to withstand and recover from the damage to their DNA caused by radiation therapy. But recent studies have shown that adding molecularly targeted agents to radiation therapy can prevent the repair of this radiation-induced damage and thereby improve the treatment response of patients with certain cancers.

Stronger, more durable responses

Although radiation is intended to destroy cancer cells by damaging their DNA, the DNA often can be repaired, resulting in only temporary responses to treatment. In some cases, radiation can actually increase the expression of cancer-driving genes such as the epidermal growth factor receptor (*EGFR*), resulting in radiation resistance. However, drugs that inhibit proteins central to cancer growth or DNA repair, such as the *EGFR* inhibitor cetuximab, can impede DNA repair and make cancer more susceptible to radiation.

“Radiation that damages DNA can be combined with a targeted drug that blocks the repair of that DNA,” said James Welsh, M.D., an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, who has led several studies in which targeted drugs

were used to overcome radioresistance in cancer. Indeed, adding cetuximab to radiation therapy has been shown to prolong overall survival in patients with head and neck cancer.

According to preclinical studies, inhibitors of PARP1 (a protein involved in repairing DNA damage) also have the potential to selectively radiosensitize cancer cells. Clinical trials of the PARP1 inhibitor veliparib in combination with radiation therapy to treat various cancers are being planned or are under way at MD Anderson and elsewhere.

Another potential therapeutic target is the hepatocyte growth factor receptor *c-Met*, which enables cellular invasion. In a recent study, non-small cell lung cancer cells in which previous radiation had induced higher *c-Met* expression levels were radiosensitized by the *c-Met* inhibitor MK-8033.

Radiosensitizing therapies can be

particularly valuable when a tumor’s proximity to sensitive structures, such as the esophagus, aorta, or brain, makes it difficult to use high doses of radiation. Dr. Welsh said, “To avoid unnecessary damage, you can use a biological approach to specifically sensitize tumor cells and increase the efficacy of radiation without increasing the toxicity to normal cells.”

With targeted agents, the ratio between the benefit from therapy and the severity of potential side effects (i.e., the therapeutic ratio) is increased. In a recent study led by Dr. Welsh, selected patients with brain metastases from non-small cell lung cancer benefited from treatment with the *EGFR* inhibitor erlotinib combined with radiation. Erlotinib (a small molecule capable of crossing the blood-brain barrier) impedes DNA repair, antiapoptotic pathways, and proliferation. Adding erlotinib to whole-brain radiation therapy in patients with brain metastases led to a median overall survival of 11.8 months, which was a significant improvement over the median overall survival of 3.9–6.0 months for historical controls. In both treatment groups, patients with *EGFR* gene mutations had a significantly longer median survival time than did patients without such mutations.

Dr. Welsh said that even within the same type of cancer, those tumors with certain gene mutations are more susceptible than others to treatment with targeted drugs plus radiation; in fact, many such treatments are effective only against cancers with specific mutations. But with recent advances in gene sequencing technology, researchers are identifying more and more targetable mutations that may identify cancers that are suitable for this type of combination treatment.

Dr. Welsh also noted that using targeted therapy to sensitize cancer to radiation and improve the response to radiation might make radiation therapy more effective in parts of the world where the latest technology is unavail-



“Radiation that damages DNA can be combined with a targeted drug that blocks the repair of that DNA.”

– Dr. James Welsh

Overcome Resistance to Radiation Therapy

able. “Radiation is an expensive technology,” he said. “The equipment and expertise for precisely targeted delivery systems such as proton therapy or intensity-modulated radiation therapy are often not available or affordable, especially in less developed countries. But if we add biological therapy to radiation, we might be able to improve the outcomes from standard radiation therapy techniques.”

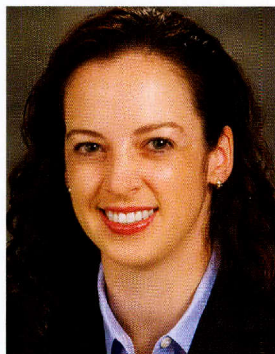
Potential for distant control

In a very small number of cases, radiation combined with monoclonal antibodies or other immunotherapies has achieved not only locoregional control but also distant, systemic control of advanced cancer by exploiting the immune system. Through a phenomenon called the abscopal effect, radiation induces antigens specific to cancer cells, priming T cells to attack cancer cells outside the radiation field.

Immunotherapy agents counter the mechanisms by which cancer cells typically protect themselves from the host’s immune system, rendering cancer cells throughout the body vulnerable to the tumor-specific T cells. Thus, in a patient with advanced disease, both the primary tumor and the metastases may respond to local irradiation of the primary tumor combined with immunotherapy.

The abscopal effect has been observed in isolated cases of melanoma, lymphoma, and kidney cancer. For example, in a few case reports of patients with metastatic melanoma, treatment with ipilimumab and stereotactic radiation not only reduced the irradiated tumor but also led to reductions in the nonirradiated tumors.

Dr. Welsh said that the abscopal effect may also yield more durable responses than cytotoxic therapy alone. “A better understanding of this type of response could lead to a future with less dependency on chemotherapy,” Dr. Welsh said. “Once T cells are primed to attack a particular cancer cell, they stay in the body and could



“[W]e’re testing the impact of hitting different places along the pathway of DNA repair in cancer cells.”

– Dr. Lauren Byers

potentially vaccinate a patient against new cancer cells.”

Lauren Byers, M.D., an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology, added that immunotherapy is also being investigated in combination with growth pathway–targeting drugs to help the immune system recognize and attack cancer cells. On the whole, cancer cell–seeking therapy has the potential to benefit patients whose cancers are resistant to radiation therapy or other treatments.

Patient selection

Targeted therapy combined with radiation therapy is being explored for patients whose cancers have a recognized gene mutation or aberrant protein for which a targeted drug is available. Many targeted drugs now exist; however, some have yet to be studied in combination with radiation.

Furthermore, enrolling a sufficient number of patients with the appropriate mutations in trials of targeted drugs with radiation therapy can be difficult. In addition to finding patients with a condition such as brain metastases from lung cancer, researchers may need to study patients who meet more selective criteria—having metastases to the brain from an EGFR-mutant non–small cell lung cancer, for example. “It’s a subset of a subset of a subset,” Dr. Welsh said of a group of patients treated with an EGFR inhibitor and radiation in a recent trial.

Still, Dr. Byers said that the rapidly accelerating development of targeted drugs is leading to more personalized treatments for an ever-increasing proportion of cancer patients. Using lung cancer as an example, she said, “Right now, about 20% of lung cancers have mutations that can be targeted by approved drugs. For some of the newer drugs, such as RET and BRAF inhibitors, we don’t have a full picture of how many patients with those mutations will benefit, but trials are under way to fill in those gaps. It won’t be long until targeted drugs for many more mutations in many types of cancer are available, and some of these drugs will likely enhance radiation therapy.”

New targets

New classes of drugs are rapidly being developed to target tumor cell and blood vessel growth, DNA repair, and other processes critical to cancer growth and spread. As more therapeutic targets are identified, more combinations of targeted drugs with radiation therapy will become available in trials. “Groups of proteins work together to orchestrate DNA repair, and we’re testing the impact of hitting different places along the pathway of DNA repair in cancer cells,” Dr. Byers said.

Matching treatments to a patient’s cancer at the molecular level also opens up new uses for existing drugs that have typically been used to treat only one or a few specific cancers. For example,

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New Test Helps Identify Glioblastoma Patients Who Could Benefit from Bevacizumab

Glioblastomas that express low levels of genes associated with mesenchymal cells may be more sensitive than other glioblastomas to bevacizumab, according to a recent study.

In a correlative analysis done as part of a phase III clinical trial, researchers led by Erik Sulman, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, sought to identify potential molecular markers for bevacizumab sensitivity in glioblastoma.

Glioblastoma is one of the most common and difficult to treat brain tumors. It is often very aggressive and has a high risk of recurrence, but the mechanisms of glioblastoma tumorigenesis and recurrence are still poorly understood. Consequently, despite much effort, the treatment options for these tumors remain limited.

Bevacizumab specifically targets vascular endothelial growth factor, which is a secreted protein involved in tumor growth and angiogenesis. It was previously known that some glioblastoma patients with recurrent tumors responded well to bevacizumab treatment and experienced longer progression-free survival and fewer symptoms than most patients with glioblastoma. This led to a multicenter phase III trial (RTOG-0825) to evaluate bevacizumab treatment for patients with newly diagnosed glioblastoma.

Dr. Sulman and colleagues sought potential molecular markers that would allow clinicians to identify which patients are most likely to respond to bevacizumab treatment. The researchers found that tumors with lower expression of some genes associated with mesenchymal cells responded better than other tumors to bevacizumab treatment. The researchers then used this information to create a predictive test for bevacizumab response.

Dr. Sulman said, “One of the key things about this predictor is that it’s designed to be used on archival tissue samples, so it doesn’t require fresh tissue.” This will allow the test to be used widely because surgical resection is the initial treatment for most patients with glioblastoma and the tissue obtained is most commonly stored as paraffin-embedded specimens.

The researchers found that tumors with lower expression of some genes associated with mesenchymal cells responded better than other tumors to bevacizumab treatment.

The results of the study were presented at the annual meeting of the American Society of Clinical Oncology in June. In the future, Dr. Sulman and his colleagues hope to validate their predictive test in additional glioblastoma patients and assess whether the method is generalizable to other tumor types. These measures could help identify patients who will respond well to bevacizumab treatment. ■

Researchers Identify Potential New Target in EGFR-Activated Cancers

Epidermal growth factor receptor (EGFR), a well-known cancer drug target, regulates MCM7, a protein vital to the first step in DNA replication, a team led by researchers at The University of Texas MD Anderson Cancer Center reported.

MCM7 is important to DNA licensing, the initial step in DNA replication. MCM7’s function—which is

often deregulated in human cancers—had not previously been tied to EGFR signaling, which leads to DNA synthesis and cell growth. The researchers found that EGFR activated MCM7 by activating another signaling molecule, Lyn.

“We established that this signaling pathway correlates with EGFR status and poor survival in breast cancer patients,” said Mien-Chie Hung, Ph.D., a professor in and chair of the Department of Molecular and Cellular Oncology and the study report’s senior author.

The researchers assessed the expression statuses of activated Lyn and MCM7 in tumor samples from breast cancer patients, and Kaplan-Meier analyses revealed that the overall survival rates of patients with low expression of either activated protein were significantly higher than those of patients with high expression of either activated protein. Seventy-five months after the completion of their initial therapy, about 60% of patients with high levels of activated Lyn or MCM7 expression were alive, whereas more than 80% of those with low levels of activated Lyn or MCM7 expression were alive.

In a mouse model of breast cancer, the researchers found that mice with high expression of either Lyn or MCM7 had tumor volumes that were two to three times larger than those of mice with low expression of either molecule.

Dr. Hung said, “Lyn overexpression might be indispensable for cancer cells that rely on EGFR signaling to proliferate,” which suggests that Lyn is a promising therapeutic target in EGFR-activated cancers. Drugs that target EGFR often become less effective over time, he noted, so Lyn provides a potentially effective target downstream from EGFR.

Lyn inhibitors have been tested preclinically and in an early-stage clinical trial. Combining Lyn and EGFR inhibitors could have a synergistic effect on EGFR-driven cancers.

The study’s findings were published in the June issue of *Cancer Cell*. ■



Depression in Cancer Patients

Managing depression improves quality of life and possibly cancer treatment outcomes

Depression is a major public health problem, as one in five Americans suffers from depression symptoms at any given time.

The risk of depression is even higher for cancer patients, who are three times more likely to develop depression than the general population. For cancer patients with uncontrolled pain, the risk for depression is even higher.

Cancer patients face many emotional challenges, such as changes in body image, intellectual function, or social function. Patients also may have concerns about death and feelings of disappointment, remorse, or hopelessness. These challenges, along with treatment side effects, can contribute to depression.

Depression and its symptoms

Depression ranges from an everyday emotion to a debilitating mental and physical condition; it can appear as a response to a particular situation or as a chronic disease that goes into remission but can resurface at any time.

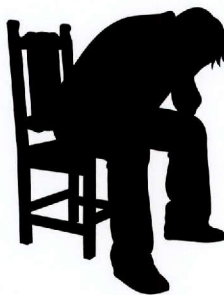
The symptoms of depression include:

- depressed mood,
- lack of interest in formerly enjoyed activities,
- significant changes in appetite or sleep patterns,
- fatigue,
- inability to think or concentrate,
- indecisiveness,
- and recurrent suicidal thoughts.

A person who has several of these symptoms (or either of the first two) for more than 2 weeks may have clinical depression. Left untreated, 66% of clinically depressed people will recover within a year, and 80% recover within 2 years.

Depression and cancer

Unfortunately, many of the symptoms of depression are also side effects of cancer or its treatment, making depression difficult to diagnose in cancer patients. To make matters worse, many



cancer treatments—including chemotherapy drugs, radiation therapy, and surgery—can cause depression or symptoms that mimic depression.

However, many patients do not report their mental health status to their oncologists.

“The stigma associated with mental illness is such that patients may not volunteer that they are in distress because of shame or fear of compromising treatment,” said Alan D. Valentine, M.D., chair of the Department of Psychiatry at The University of Texas MD Anderson Cancer Center and an expert on depression and cancer. Dr. Valentine added, “Some clinicians assume that depression is a normal part of the cancer experience and thus need not be addressed.”

However, untreated depression has many negative effects on cancer patients. Depression can increase the length and cost of hospitalization, delay treatment, result in treatment noncompliance (such as missing appointments or forgetting to take medicine), and increase stress for caretakers. The most serious danger posed by untreated depression is suicide. Cancer patients are twice as likely as the general population to take their own lives.

Research and treatment

Depression can also physically affect the cancer itself. Several studies have demonstrated that patients affected by depression, stress, and inadequate social support have higher levels of cancer-causing proteins (interleukin-6 and vascular endothelial growth factor) than do patients who have a positive outlook and good social support.

Studies from the past decade in patients with lung cancer, breast cancer, and brain cancer found that depression

had a negative impact on overall survival and disease-free intervals.

Depression, however, can be managed effectively in cancer patients. A study from 2011 showed that behavioral interventions prolong survival for cancer patients. These interventions can include methods such as counseling, cognitive behavioral therapy, and antidepressant drugs.

In counseling and cognitive behavioral therapy, physicians or counselors help their patients learn successful strategies for coping with stress and creatively adapt these strategies to address each patient’s current circumstances.

Prescriptions for antidepressants should be carefully coordinated with cancer treatments, as some drug combinations have adverse effects. However, not all side effects are negative; some antidepressants have side effects, such as increased appetite, that can be used to the advantage of cancer patients.

Dr. Valentine emphasized that depression is common, but not normal, in patients with cancer. “That treatment of depression improves quality of life for cancer patients and caregivers is not in dispute,” he said. “There is increasing, encouraging research evidence that such treatment also confers a survival benefit.”

Any cancer patient who has signs of depression should not hesitate to tell his or her doctor; controlling depression can improve or even save the patient’s life. ■

—J. Delsigne

FOR MORE INFORMATION

- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
- To hear an interview with Dr. Valentine, visit *Cancer Newsline* at <http://www.mdanderson.org/newsroom/cancer-newsline/cancer-newsline-topics/2011/cancer-newsline-double-trouble-cancer-and-depression.html>

Targeted Cancer Therapies

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trastuzumab, a monoclonal antibody used in the treatment of breast cancer to block the HER2 cell surface receptor, may also improve outcomes from radiation therapy in some patients with esophageal cancer.

However, the many treatment possibilities presented by targeted drugs need to be narrowed down to effective, safe treatment strategies. Key targets for specific cancers need to be validated in clinical trials of new targeted drugs given individually and in combination with radiation, chemotherapy, or other targeted drugs. The schedules on which different treatment modalities should be given need to be determined—whether a drug should be given before or after radiation, for instance.

Another concern to be addressed by researchers is that drugs combined with radiation may give rise to complications that do not occur with either treatment alone (e.g., tracheal-esophageal fistula from bevacizumab with radiation).

“[Y]ou can use a biological approach to specifically sensitize tumor cells and increase the efficacy of radiation without increasing the toxicity to normal cells.”

– Dr. James Welsh

“It’s a very exciting time because of all the new targets that are out and all the new data we’re getting on patients’ tumors,” Dr. Welsh said. “But figuring out how to use these drugs properly is a challenge we need to undertake methodically with organized studies so that we can learn how to do this in a safe and effective manner.” ■

FOR MORE INFORMATION

Dr. James Welsh 713-563-2447

Dr. Lauren Byers 713-792-6363

FURTHER READING

Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567–578.

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