

REPORT TO PHYSICIANS

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Oncology

IMAGING NERVES

By John LeBas

Unintentional damage to nerves remains a significant problem in cancer treatment. Many cancer treatments can potentially harm nerves, resulting in neuropathies with such symptoms as impotence, weakness, abnormal sensations, and difficulties with bowel control and bladder function. Many of these problems might be prevented if peripheral nerves could be made visible, but currently there are very few options for visualizing peripheral nerves in vivo.

Recent research at The University of Texas M. D. Anderson Cancer Center points to a potential solution. Using laboratory animals, M. D. Anderson investigators have demonstrated a way to make peripheral nerves literally light up with fluorescent imaging. The work is believed to be the first demonstration of nerves preferentially taking up

Tetanus Toxin Offers Promise for Neurography

*The goal of neurography is in vivo imaging of nerves,
as suggested by this artist's rendering.*

“Our experiments showed that that we could hijack the retrograde transport mechanism by using this tetanus toxin fragment to carry imag-

a contrast agent to enhance visualization, which has researchers excited about its potential not only in cancer treatment but in other health care applications as well.

The novel imaging approach taps into a natural nerve transport pathway usually used for the growth and maintenance of nerves. “This retrograde transport pathway is what the neuron itself uses to get growth factors back from peripheral tissue to the brain or spinal cord,” said Dawid Schellingerhout, M.D., an assistant professor in Diagnostic Radiology and Experimental Diagnostic Imaging at M. D. Anderson and lead investigator on the studies.

It turns out that a non-toxic fragment of tetanus toxin can bind to this pathway and be transported up the nerve. Dr. Schellingerhout realized that an image-enhancing agent could be attached to this fragment and transported along nerves as well, essentially hitching a ride and making the path visible.

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Tetanus Toxin Offers Promise for Neurography

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Improved diagnostic ability has always led to improved therapies. With proper contrast agents and imaging, we may be able to improve our understanding of nerve-related diseases to the point where we can offer effective therapies.”

— Dr. Dawid Schellingerhout

ing agents into nerves, bypassing the shielding effect of the blood-brain barrier,” he explained. It is the protective wall formed by the blood-brain barrier that makes delivering therapies and imaging agents to nervous system components so difficult.

“Most would agree that our imaging technologies for peripheral nerve structures could benefit from a major improvement,” Dr. Schellingerhout continued. “We’re just not that great at imaging peripheral nerves. We can use magnetic resonance (MR) to show nerves near the spinal cord, but that’s about it.

“Contrast that with cardiovascular imaging, for which effective imaging technologies developed owing to the successful application of contrast agents. Thanks to those imaging technologies, we can do a vast range of diagnostic and therapeutic procedures such as angiograms, computed tomography angiograms, endovascular procedures, and so on. A whole industry grew out of these imaging techniques, and because we do such a good job of imaging vessels, we can help thousands of people each day.”

If nerves could be imaged in a similar manner, people with blindness, deafness, paralysis, impotence, diabetic foot ulcers, neuropathies, and other nerve-related problems could benefit. “History teaches us that improved diagnostic ability has always led to improved therapies and eventually to better outcomes,” Dr. Schellingerhout said. “Many nerve-related diseases are currently regarded as without cure, but with proper contrast agents and imaging, we may be able to improve our understanding of

these diseases to the point where we can offer effective therapies.”

Scope of the problem

The need for effective nerve imaging in human patients is as vast as the number of ailments caused by injured or diseased nerves. Unfortunately, advances in neurography, or the imaging of nervous system components, have been slow. Unlike blood vessels, into which compounds can be injected for transport, the nervous system consists of solid tissues with no built-in channel for transporting agents.

What this means for imaging is that there is no way to distribute a contrast agent throughout the nervous system. And without a contrast agent, the ability of current imaging technologies like MR and computed tomography to distinguish nerves from surrounding tissue is greatly restricted—particularly as nerve bundles become smaller the farther they are from the brain and spine.

In surgery, whether for cancer or other conditions, nerves are often inadvertently damaged or cut because of visualization difficulties or the nerves’ proximity to other structures that must be disturbed. For example, 75% or more of men who undergo prostatectomy for the treatment of prostate cancer suffer postsurgical impotence resulting from nerve damage during surgery. “Visualizing the nerve bundle is actually not a problem for the expert surgeon,” explained John W. Davis, M.D., an assistant professor in the Department of Urology who conducts prostatectomies using robotic-assisted techniques. “However, multiple blood vessels crossing from the nerve bundle to the prostate

must be divided and clipped during prostatectomy, and it is thought that the stretching and traction on the bundle causes injury, even if the nerves are not cut.

“Can a surgeon do a better job of preserving potency if the actual nerve fibers can be seen distinctly from their surrounding bundle of blood vessels? Further study will be required, but the idea is certainly attractive,” continued Dr. Davis, who is not involved with Dr. Schellingerhout’s work. “Perhaps this method of neurography could show the surgeon where the nerve fibers are closest to the prostate gland and where they are not, such that the surgeon could prioritize time and techniques more appropriately. We may even learn more about the variability of nerve fiber anatomy.”

The other mainstays of cancer treatment, chemotherapy and radiation therapy, can also cause nerve injuries with significant consequences for the patient. Certain chemotherapies, particularly platinum-based agents, can induce severe, painful neuropathy. Radiation can cause such conditions as brachial plexopathy (occurring in some patients receiving treatment for thoracic and breast tumors) when nerves in or adjacent to the treatment area are damaged by radiation (although the peripheral nervous system is relatively radioresistant).

Finally, cancer itself often directly invades or interferes with nerve tissue adjacent to the primary tumor. Furthermore, the spine and brain are common sites of metastasis for numerous cancer types. Yet little can be done to visualize

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Fight-or-Flight Hormones Linked to Metastasis

Ovarian cancer cells that break away from the primary tumor are protected by heightened levels of two stress hormones, a research team at M. D. Anderson Cancer Center recently discovered. The finding links chronic stress to the ability of ovarian cancer cells to metastasize.

In preclinical research, the team found that heightened levels of the fight-or-flight stress hormones epinephrine and norepinephrine permit more malignant cells to safely leave the primary tumor, a necessary step in metastasis and cancer progression. Researchers also found that ovarian cancer patients die earlier when the FAK protein, which is activated by the hormones, is present at high levels in their tumors. Further, depressed patients were found to have higher levels of FAK.

"When normal cells become detached from neighboring cells or from the supportive scaffolding known as the extracellular matrix, they die from anoikis, a form of programmed cell death," said first author Anil Sood, M.D., a professor in the Departments of Gynecologic Oncology and Cancer Biology. "Cancer cells find a way to bypass anoikis, so they survive as individual cells circulating in the blood or in ascites." Resistance to cell death helps malignant cells migrate from the primary tumor and reattach to colonize new sites.

"Restoring cancer cells' vulnerability to anoikis would open a new avenue for suppressing tumor growth and metastasis," Dr. Sood said. Two promising approaches—directly silencing FAK or using beta blockers to preempt its activation—worked in cell culture and mouse models, making them candidates for human use.

The team showed that increases in epinephrine, also known as adrenaline, and norepinephrine reduced the number of ovarian cancer cells killed by anoikis by activating FAK. The researchers previously showed that FAK is abundantly present in ovarian cancer cells.

Lab experiments showed that resist-

ance to cell death by anoikis begins when one of the hormones connects with the β 2-adrenergic receptor (ADRB2), which activates FAK via other intermediate proteins. Treating cells with beta blockers to inhibit the ADRB2 connection or using small interfering RNA (siRNA) to shut down FAK increased cell death.

In a mouse model of human ovarian cancer, mice subject to restraint stress had smaller tumors with fewer nodules and greater cell death when treated with siRNA to suppress FAK. Treatment with the beta blocker propranolol had a similar effect.

The researchers examined 80 cases of invasive epithelial ovarian cancer to assess the role of stress-induced FAK activity. They found increased FAK expression in 67% of patients and heightened levels of phosphorylated FAK in 50%.

Patients with high levels of either measure had greatly reduced overall survival over 3 years. About 65% of those with low FAK expression survived at least 3 years compared with 30% of those with high expression. For activated FAK, the values were 65% compared with about 15%.

Using depression as an indicator of stress, the researchers found major depression was associated with higher levels of activated FAK and increased levels of norepinephrine in the tumors.

The research was published in *Journal of Clinical Investigation*. ●

Drug Combination Shows Promise for Colon Cancer Chemoprevention

A two-drug combination destroys precancerous colon polyps with no effect on normal tissue, opening a new potential avenue for chemoprevention of colon cancer, a team of M. D. Anderson scientists reported recently in *Nature*.

The regimen, tested so far in mouse models and on human colon cancer tissue in the lab, appears to address a problem with chemopreventive drugs—

"This combination would be a new approach to chemoprevention."

— Dr. Xiangwei Wu

they must be taken continuously over the long term to be effective, exposing patients to possible side effects, said senior author Xiangwei Wu, Ph.D., an associate professor in the Department of Head and Neck Surgery.

"This combination can be given short term and periodically to provide a long-term effect, which would be a new approach to chemoprevention," Dr. Wu said.

The team found that a combination of vitamin A acetate (RAc) and TRAIL, short for tumor necrosis factor-related apoptosis-inducing ligand, kills precancerous polyps and inhibits tumor growth in mice that have deficiencies in a tumor-suppressor gene. That gene, adenomatous polyposis coli (APC), and its downstream signaling molecules are mutated or deficient in 80% of all human colon cancers, Dr. Wu said.

Early experiments with APC-deficient mice showed that the two drugs given in combination or separately did not harm normal colon epithelial cells. And given separately, the drugs showed no effect against adenomas, or premalignant polyps.

However, RAc and TRAIL given together killed adenoma cells via apoptosis, a form of programmed cell death. RAc, researchers found, sensitizes polyp cells to TRAIL. Reduction in polyps was first seen in experiments using mice; follow-up studies with biopsy samples from patients with familial adenomatous polyposis showed that treatment of normal tissue caused little cell death, while 57% of polyp cells were killed via apoptosis.

Before human clinical trials can be considered, Dr. Wu said, the team will conduct additional research to identify potential side effects and also will try to develop an injectable version of the combination. ●

Early Uterine Papillary Serous Carcinoma

Treatment Options Tailored to Patient and Disease Characteristics

By **Sunni Hosemann**

Introduction

Uterine papillary serous carcinoma (UPSC) comprises 5%–10% of newly diagnosed endometrial cancers. Some UPSC tumors, when found early, will appear to be confined to a small uterine polyp, with no invasion into the wall of the uterus. Nonetheless, patients with such tumors should be referred to a gynecologic oncologist for a more extensive initial surgical staging and treatment planning than women with other uterine cancers may require.

Following surgery, a decision must be made about the next steps in treatment. The range of choices among current standards is wide, from no further treatment (observation) to radiation and/or chemotherapy. “It’s either nothing or a lot,” explained Karen Lu, M.D., a professor in the Department of Gynecologic Oncology at The University of Texas M. D. Anderson Cancer Center. The range of options for early-stage UPSC stems from the question: Which patients require substantial adjuvant (postoperative) therapy, and which patients should only be observed?

According to Lois Ramondetta, M.D., an associate professor in the Department of Gynecologic Oncology, the wide range of treatment choices is confusing and reflects the relative paucity of data specific to this variant of endometrial cancer. “Most large trials have combined all endometrial cancers, and owing to the relative rarity of individual histologic subtypes, it is difficult to accrue significant study populations in order to study a specific subtype,” Dr. Ramondetta said. In general, though, based on reviews of recent studies, physicians at M. D. Anderson rarely choose observation alone for women with early-stage UPSC and instead favor not one but a combination of adjuvant therapies.

Understanding UPSC

UPSC is associated with a high risk of recurrence and accounts for 39% of deaths resulting from endometrial cancer. That statistic suggests UPSC should be treated differently than other endometrial cancers, but deriving evidence-based guidelines for UPSC-specific treatments has been difficult. Because of the rarity of UPSC, few studies targeting this disease subtype have been conducted.

The more common variants of endometrial carcinoma are classified as type I cancers. They have an endometrioid histology, are more typically seen in younger women, and are associ-

ated with obesity and hyperestrogenism. UPSC is categorized as a type II endometrial cancer, is seen more commonly in older, thinner women, and is not historically associated with hormonal risk factors. The incidence of UPSC is also significantly higher in African-American women and in women who have had breast cancer. Type II endometrial cancers carry a worse prognosis than type I cancers, regardless of stage at presentation.

The most important difference between type I and type II endometrial cancers is their behavior. Type I endometrial tumors tend to progress by invading local tissues before metastasizing via the lymphatic and vascular systems. UPSC, on the other hand, spreads to peritoneal surfaces, much like ovarian cancer, and thus the depth of tumor invasion is not a reliable indicator of whether UPSC has metastasized. In fact, many UPSCs manifest as a polyp-like structure—a tumor on the end of a stalk—with no apparent invasion into endometrial tissue. Further, in some cases the disease appears to be confined to just a single polyp. This appearance belies the danger of UPSC: evidence of extrauterine disease is found in as many as 40% of patients in whom no myometrial invasion was present; and not only is the recurrence rate for stage I UPSC much higher than that for endometrioid tumors, but recurrence is also more likely to be distant than local.

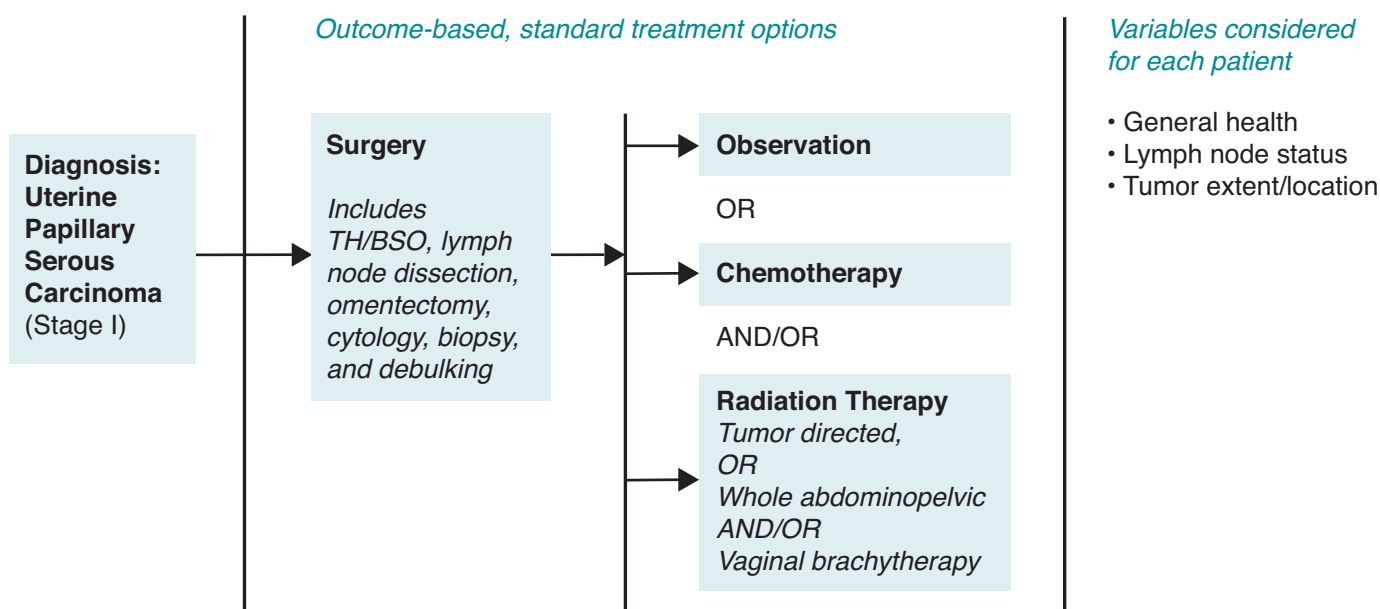
When UPSC does recur at distant sites, it becomes more difficult to treat, Dr. Lu said. Recurrence of type I disease is most commonly local—within the pelvis—and is often treatable with radiation therapy.

Many endometrial tumors display a mixed histology. Although it was thought in the past that at least 10% papillary serous histology should be present to warrant a diagnosis of UPSC, studies have demonstrated that the tendency to recur and survival are related not to the percentage of tumor that has papillary serous histology but rather to the presence of any papillary serous component. Therefore, specialists at M. D. Anderson believe that endometrial tumors with any papillary serous component, no matter how small, should be treated as UPSC.

Initial Treatment

Treatment of all endometrial cancers begins with surgery, including a total hysterectomy; removal of ovaries, fallopian tubes, and aortic and pelvic lymph nodes; and examination of the abdomen for evidence of extrauterine disease. For UPSC, the surgery may be more extensive, and like the surgical staging of ovarian cancer, it includes removal of the omentum, scrutiny

Early Uterine Papillary Serous Carcinoma: Primary Treatment Options



of all peritoneal surfaces for evidence of tumor, excision of all noted disease (“debulking”), and washings and biopsies for pathologic examination. This is an extensive operation that, like many operations for gynecologic cancers, should be performed by a gynecologic oncologist.

When UPSC is confirmed by surgical-pathologic staging to be stage I, standard options for further treatment range from observation to adjuvant chemotherapy and/or radiation therapy.

Adjuvant Treatment Decisions

Overview

At M. D. Anderson, a patient’s general health status is the overarching determinant of the approach to treating UPSC. Lymph node status and tumor characteristics are considered in the assessment of recurrence risk but are less reliable indicators of recurrence risk in UPSC than in some other endometrial cancers. These characteristics may, however, help the physician tailor therapy, particularly radiation treatments.

Observation

Currently, many guidelines and standard treatment recommendations include the option of observation following surgery for stage IA UPSC. In light of recent studies, however, physicians at M. D. Anderson recommend adjuvant treatment for all patients with a diagnosis of UPSC, unless the patient has concomitant medical issues that would significantly tip the risk/benefit ratio—in other words, a comorbidity or perform-

ance status that would make additional therapy less feasible.

The driving force behind treatment decisions for UPSC is its propensity to recur. As previously mentioned, UPSC’s recurrence risk is not indicated by tumor size, extent, or depth of invasion. According to Dr. Lu, serous malignancies can be aggressive regardless of the amount of tumor present. “The recurrence risk and patterns are the main reason why we would be very nervous about recommending observation alone,” she explained. “Even when there is no sign of invasion, we know now that UPSC spreads in other ways and has a high recurrence rate.” However, added Dr. Ramondetta, “It’s hard to tell a patient who has a disease confined to a polyp that she needs extensive treatment, especially if there is just a small percentage of serous histology present.”

But recurrences of UPSC are likely to occur at distant sites such as the lung—a much greater threat than local recurrence. Treatment decisions for an individual patient, therefore, include weighing her tolerance for adjuvant treatments against the possibility of an incurable recurrence.

Chemotherapy

Until recently, chemotherapy was rarely used for early-stage endometrial cancer that appeared to be confined to the uterus. However, since chemotherapy offers the best chance of eradicating distant disease and since UPSC is associated with distant recurrence, chemotherapy is now a part of the standard adjuvant therapy for all stages of UPSC except stage

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IA. For stage IA UPSC, chemotherapy is recommended as an adjuvant therapy.

Radiation

Radiation therapy is a traditional adjuvant treatment for endometrial cancers and is known to reduce the incidence of recurrence in the pelvis. For stage I UPSC, there are several options for adjuvant radiation therapy, including abdominopelvic or pelvic radiation with or without vaginal brachytherapy (which provides a vaginal “boost” dose of radiation) or vaginal brachytherapy alone.

National Comprehensive Cancer Network guidelines recommend tumor-directed radiation therapy (defined as radiation to the area of tumor involvement but not to the whole abdomen) as an option for stage IA UPSC. For stage IB and IC UPSC, the guidelines recommend either pelvic or abdominopelvic radiation, with or without vaginal brachytherapy. According to Anuja Jhingran, M.D., a professor in M. D. Anderson’s Department of Radiation Oncology, the vagina is the most common site for local recurrences of UPSC, and therefore vaginal brachytherapy is considered an important adjunct to improve local control.

Vaginal brachytherapy is delivered via an inserted cuff; a typical regimen includes a total of 5 treatments, administered every other day, compared to 5 weeks of daily treatment for pelvic or abdominopelvic radiation. “The toxicity of pelvic radiation is a key consideration,” Dr. Jhingran said. “With the vaginal cuff, there are minimal side effects since the bladder, rectum, and small bowel are not irradiated.”

Combination Therapy

Based on results from a recently completed prospective phase II study of patients with stages I-IIIa UPSC, physicians at M. D. Anderson now favor a combination approach of concurrent chemotherapy and radiation therapy followed by a course of chemotherapy for all patients with stages I-IIIa UPSC as a means of providing both local and systemic disease control.

The chemoradiation phase of treatment in the trial consisted of weekly paclitaxel plus pelvic radiation followed by vaginal brachytherapy. This was followed by a course of four cycles of paclitaxel. Improvements in overall survival and disease-free survival using this approach were seen in all stages compared to historical and published data.

Whether there are patients with early-stage UPSC who can safely forego chemotherapy or part of the radiation treatment remains to be determined. According to Dr. Jhingran, a new multicenter trial by the Gynecologic Oncology Group, a national cooperative group of the National Cancer Institute, aims to determine whether vaginal brachytherapy may be used instead of pelvic radiation therapy in select patients with early-stage UPSC. Patients in this trial will receive chemotherapy in addition to radiation.

Currently, Dr. Jhingran would consider vaginal brachytherapy with or without systemic chemotherapy in patients with stage IA or minimally invasive IB UPSC if more than 10 lymph nodes are removed at surgery and are negative for disease. In particular, this option would be considered if tolerance for additional therapy is in question based on performance status, especially in view of vaginal brachytherapy’s low morbidity and relative convenience for the patient.

Conclusion

Choosing from the rather substantial UPSC treatment options—an extensive surgery, radiation therapy, and chemotherapy, all of which carry their own risks for morbidity—remains a challenge. “We always weigh the possible consequences of treatment in conjunction with opportunities for improved overall survival for each individual patient,” Dr. Ramondetta said. “Treatment is always tailored according to what the patient can tolerate while minimizing her risk and maximizing chance for cure.” ●

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Addressing the Cosmetic Effects of Breast Cancer

Most women undergoing treatment for breast cancer will experience, at least temporarily, some change in their appearance. The measures outlined below can give such women more choices for their appearance, both during and after cancer treatment.

Breast prostheses and reconstruction

Mastectomy, the complete removal of a breast, is sometimes performed to treat breast cancer. Described below are three methods of breast reconstruction used after a mastectomy.

- **Breast prostheses.** Breast prostheses offer a simple cosmetic solution for women who have had a mastectomy. Made of materials such as foam or silicone, these devices can be sewn into the lining of a bra or attached to the chest with adhesive, creating symmetry with the other breast. Many prostheses have the same weight as the remaining breast to reduce the feeling of “lopsidedness” and to minimize back strain.
- **Breast implants.** Implants filled with saline or silicone gel can be inserted into the chest to create a new breast. The procedure is often performed on an outpatient basis and is cheaper than reconstruction using the patient’s own tissue (discussed next). However, because they are synthetic, implants can leak or rupture and may need to be replaced at least once in the woman’s lifetime.
- **Tissue flap reconstruction.** Another type of breast reconstruction uses a segment of tissue (muscle, fat, and/or skin) taken from the abdomen or upper back to form a new breast. Surgeons can sometimes reconstruct the nipple to make the reconstructed breast look more natu-

For more help on improving your appearance during and after breast cancer, visit www.lookgoodfeelbetter.org.

ral. Because a flap uses the woman’s own tissue, the reconstruction often feels more natural than an implant. However, reconstruction is more expensive and can involve more pain and a longer recovery than an implant procedure.

Lymphedema

Sometimes, breast cancer treatment causes lymphedema—a swelling caused by the buildup of an immune system fluid called lymph. Lymphedema results when the lymph vessels that normally drain lymph away are damaged during treatment, allowing the lymph to collect under the skin. Lymphedema can be painful and disfiguring, but many patients are able to find relief by carefully managing their condition:

- Massage and other techniques can keep lymph moving and reduce buildup.
- Preventing infection and other physical strain can help prevent lymph buildup from worsening.
- Comfortable clothing can improve the swelling.

Ask your doctor or nurse for more detailed information on treating lymphedema. In many locations, support groups and counseling are available as well.

Hair loss

Many chemotherapy drugs cause hair loss—from the scalp, face, and body. Chemotherapy-related hair loss (alopecia), which usually begins 7 to 21 days after the start of treatment, is temporary and can be concealed. Some tips for dealing with the loss of hair are outlined below.

- Some women prefer to wear a wig. Ideally, a wig should be selected before hair loss begins so that it can be matched to the woman’s natural hair color. A quality synthetic hairpiece can cost up to \$500 and may be covered by insurance.
- Hats and scarves are a popular choice, since many styles and matching options are available.
- Hair eventually will regrow, although it may have a different look or texture. When the hair begins to grow back, only mild shampoos should be used. Styling techniques and products should be avoided, since they may damage the new hair.

Cosmetics and skin care

Dry or sallow skin sometimes results from breast cancer or treatment side effects. Moisturizers and cosmetics can be used to treat or conceal such skin problems.

Cosmetics can also be helpful in recreating eyelashes and eyebrows and changing one’s overall appearance. ●

For more information, talk to your physician, or:

- visit www.mdanderson.org
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Tetanus Toxin Offers Promise for Neurography

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the physical effects of tumors on nerves, particularly small nerves, or to deliver therapies to tumors that directly involve nerves.

Beyond cancer, the medical need for nerve imaging is widely apparent. For example, diabetics often suffer neuropathy that prevents them from feeling their feet. Because of insensate feet, many of these patients develop infected foot ulcers that can be very difficult to cure, sometimes requiring surgery and even amputation. "Unfortunately, diabetic neuropathy can currently be treated only by improving control of the underlying diabetes and stopping its progression," Dr. Schellingerhout said. "Current knowledge suggests that the damage already done is irreversible. As with the damage to nerves caused by cancer and cancer therapies, we need to be able to visualize the nerves to better decipher the mechanisms at work in causing the damage. Having a means to study the retrograde transport pathway in nerves is almost certain to yield new insights into the causes and potential cures for these neuropathies."

Hijacking the tetanus toxin

The retrograde transport pathway has long been known as the mechanism by which growth factors move along peripheral nerves to the nerve cell bodies in the brain and spine. Work done previously to understand tetany revealed that tetanus

toxin also makes use of the retrograde transport pathway to gain access to the spinal cord. Further work in deciphering functions of the various parts of tetanus toxin revealed that a fragment of the toxin can be transported without the toxic effects of the intact toxin. "Thus, this nontoxic fragment can be labeled with useful compounds and can deliver them efficiently along the nerves," Dr. Schellingerhout said.

In a report published last fall in the journal *Molecular Imaging* (Schellingerhout et al., v. 8, 2009), Dr. Schellingerhout and colleagues showed that the nontoxic fragment labeled with a fluorescent imaging contrast agent was specifically and quickly taken up by the sciatic nerve in mice and delivered to the spinal cord. The compound was injected into muscle and could subsequently be seen on imaging illuminating the nerve tissue along which it had traveled.

If this approach can be refined and applied to humans, it could allow nerve mapping and image-based study of nerve physiologic processes, Dr. Schellingerhout said. "This could significantly advance our capabilities in surgical planning and diagnosis of nerve disease," he explained. "We are currently gathering more data and seeking funding to make neurography in humans a reality." ●

For more information, contact Dr. Schellingerhout at 713-792-3817.

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