Robotic Surgery Makes Tissue Harvest for Breast Reconstruction Less Invasive

By Jill Delsigne

A new minimally invasive robotic procedure enables surgeons to harvest latissimus dorsi muscle flaps for breast reconstruction with less scarring and discomfort than traditional techniques.

Breast reconstruction after a total or partial mastectomy often employs a pedicled latissimus dorsi muscle flap. The latissimus dorsi is an ideal muscle for breast reconstruction because it is large, flat, and able to cover an implant and because other muscles in the back can compensate for the loss of latissimus dorsi muscle function. However, in a traditional latissimus dorsi muscle harvesting procedure, the surgeon dissects through the skin and fat of the back to reach the muscle, leaving a large scar (15–40 cm) across the patient’s back, even when no skin is needed for the reconstruction. In addition to patients’ aesthetic concerns about such a

Dr. Jesse Selber (right) observes as surgeons position the robot for a minimally invasive robotic latissimus dorsi muscle flap harvest and breast reconstruction.
large and visible scar, the tightness of the skin around the scar can be painful and can limit mobility.

To address these issues, Jesse C. Selber, M.D., an assistant professor in the Department of Plastic Surgery at The University of Texas MD Anderson Cancer Center, developed a robotic surgical procedure for latissimus dorsi muscle harvest that does not leave the conspicuous scars associated with the traditional technique. “It didn’t make sense that plastic surgeons—who should be the most concerned of any specialists about aesthetic outcomes—did not have tools to minimize the invasiveness of the procedures we do,” he said.

The robotic procedure

Dr. Selber’s robotic procedure involves making an incision of about 5 cm in the axilla. If the patient had a sentinel lymph node biopsy, the biopsy incision site can be reused to avoid creating any additional incisions and scarring.

Robotic arms are inserted into the patient through three ports. The first port is placed at the lower end of the axillary incision, and the next two are placed through smaller incisions made 12–13 cm apart in front of the edge of the latissimus dorsi muscle. The robot’s endoscopic camera is inserted through the middle port, which is about 1 cm wide. The other two ports, which are both about 8 mm wide, allow the passage of the robotic arms into the space where the muscle can be dissected. The tools used to harvest the flap are a Cadicere grasper, monopolar scissors, and an electrocautery clamp.

The surgeon controls the movements of the robotic arms through a console several feet from the patient. The camera feed provides three-dimensional, high-resolution images, enabling the surgeon to identify and avoid damaging the blood vessels that are necessary for the survival of the latissimus dorsi muscle. The surgeon uses the electrocautery clamp to minimize bleeding and dissect through the cobweb-like thoracolumbar fascia.

When the surgeon has separated the latissimus dorsi muscle from the surrounding tissue, the pedicled flap is transferred under the skin from the back into the breast while remaining connected to its blood supply at the pivot point in the axilla.

Advantages and limitations

Dr. Selber has performed this surgery in breast cancer patients who have had lateral lumpectomies and nipple-sparing mastectomies as well as in patients with a tissue expander who were preparing to receive radiation therapy and needed protection for the permanent implant. He has also used the robotic procedure to harvest latissimus dorsi free flaps in patients undergoing scalp or extremity reconstruction.

After performing more than a dozen
Much of the technology used in robotic surgery was developed by the National Aeronautics and Space Administration to provide medical treatment for astronauts in space and by the Defense Advanced Research Projects Agency to provide remote surgical care for soldiers. However, both of these government agencies decided not to pursue the technology. Instead, private companies continued to develop the technology.

The da Vinci Surgical System, approved by the U.S. Food and Drug Administration (FDA) in 2000, is currently the world’s most widely used robotic surgical system. The da Vinci system is used in more than 2,000 hospitals, including MD Anderson. Physicians have applied this technology to numerous procedures, including prostatectomies (see Oncolog, March 2012), gynecological procedures, and cardiac valve repair. Although commonly referred to as robotic latissimus dorsi muscle flap harvests, Dr. Selber has not encountered any robot-specific complications, has not had any flap compromise, and has not ever had to convert to an open procedure.

The dissemination of robotic plastic surgery techniques has been slowed by the limited access to robotic equipment in the operating room and the difficulty of learning to use the equipment effectively. In addition to learning how to operate the robot, surgeons also must be able to troubleshoot when the machine does not function optimally or when circumstances require a modification of the procedure. Dr. Selber practiced his robotic plastic surgery procedure for 2 years in the laboratory to perfect his technique before attempting it on a patient. After several successful procedures, he began training other surgeons to use the technique.

So far, Dr. Selber has begun to train three other MD Anderson plastic surgeons—in addition to the fellows he works with—in robotic tissue harvest. The robot’s dual-console set-up allows the surgeon who is being trained to see exactly what the operating surgeon sees, and control of the operating instruments can be switched back and forth to gradually increase the trainee’s responsibility. In Dr. Selber’s experience, as surgeons practice this technique, robotic harvest time decreases from more than 2 hours to about 1 hour.

The U.S. Food and Drug Administration (FDA) has not approved the use of robotic surgical instruments for harvesting tissue for breast reconstruction, and patients are informed that such use is considered off-label. However, Dr. Selber has demonstrated that his robotic flap harvest technique is safe and effective, and he and MD Anderson have submitted an application to the FDA for an investigational device exemption so they can begin a clinical trial that would create a path to the procedure’s approval.

Dr. Selber is also developing micro-surgical techniques that take advantage of the robot’s enhanced precision and optics; these include robotic techniques for suturing small blood vessels and anastomosing small lymphatics.

FOR MORE INFORMATION
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FURTHER READING


Diagnosis and Treatment of Invasive Fungal Infections in Patients with Hematological Malignancies

By Bryan Tutt

Invasive fungal infections are important causes of morbidity and death for patients with hematological malignancies. Although much progress has been made in the management of opportunistic fungal infections, their diagnosis and treatment remain a challenge.

Many leukemia and lymphoma patients receive high-dose chemotherapy, sometimes followed by stem cell transplantation, compromising their immune systems. As a result, invasive fungal infections occur in 8%-10% of patients with hematological malignancies. “Because these patients can’t mount an effective immune response, the resulting death rate from many of these infections is over 50%,” said Dimitrios Kontoyiannis, M.D., a professor in the Department of Infectious Diseases at The University of Texas MD Anderson Cancer Center. He added that fungal infections can be a contributing cause of death in patients for whom an infection causes chemotherapy to be attenuated or withheld.

Types of fungal infections

Dr. Kontoyiannis, whose clinical practice and research are focused on the diagnosis and treatment of fungal infections, said the most common invasive fungal infections in patients with hematological malignancies are aspergillosis and candidiasis.

The genus Aspergillus comprises several hundred species that are ubiquitous in the environment but pose little threat to people with healthy immune systems. Immunocompromised patients, however, are more vulnerable to infection by Aspergillus fumigatus or (to a lesser degree) other Aspergillus species.

Invasive candidiasis occurs in immunocompromised patients when Candida yeasts colonizing the body enter the bloodstream. In patients with hematological malignancies, this often occurs in the digestive system, where beneficial bacteria that normally inhibit the growth of yeasts have been destroyed by antibiotics. Candida infections also may occur at catheter insertion sites.

Less common invasive fungal infections, such as cryptococcosis or mucormycosis, also pose a threat to patients with hematological malignancies.

Diagnosis

The nonspecific symptoms of invasive fungal infections can impede timely diagnosis. For example, the most common symptom of invasive candidiasis is persistent fever.

Invasive aspergillosis manifests primarily as pneumonia or sinus infections, with symptoms consistent with those conditions, or as relatively asymptomatic lesions in the lung parenchyma. However, invasive aspergillosis can progress rapidly and disseminate hematogenously.

Fungal infections of the airway may be detected by chest radiography or, at an earlier stage, by computed tomography. Because it is not always possible to distinguish between fungal and bacterial infections on imaging studies, bronchoscopy may be used to better visualize the infected area and to obtain tissue samples.

Cultures of tissue, blood, or other fluids are used to make a definitive diagnosis of invasive fungal infections; however, these tests are slow, so treatment may be initiated empirically based on clinical suspicion. Also, comorbid conditions preclude tissue biopsy in some patients with hematological malignancies, and previous treatment with antifungal drugs can make a specific fungal diagnosis difficult.

For these reasons, researchers are developing new diagnostic tests using serum markers. For example, an enzyme-linked immunosorbent assay that detects galactomannan, a component of the Aspergillus cell wall, has been approved by the U.S. Food and Drug Administration for use with serum samples. Serum polymerase chain reaction tests can identify fungal species quickly and accurately, but these tests are not yet routinely used to diagnose fungal infections. Dr. Kontoyiannis is leading two clinical studies of a novel magnetic nanotechnology for the diagnosis of candidiasis at a much earlier stage than is possible with the conventional, blood culture–based tests.

Treatment and prevention

Until the mid-1990s, amphotericin B deoxycholate was the mainstay for treating invasive fungal infections. In the past 2 decades, physicians have witnessed an explosion of effective and less toxic drugs to treat these infections. Specifically, the less nephrotoxic lipid formulations of amphotericin B, the extended-spectrum azoles (such as voriconazole and posaconazole), and the echinocandins (which inhibit fungal cell wall synthesis) are also now commonly used for treatment and prophylaxis.

Antifungal prophylaxis is effective for patients considered at high risk for invasive fungal infections, such as leukemia patients and stem cell transplant recipients; however, guidelines for prophylaxis vary among institutions. New-generation azoles are currently commonly used for prophylaxis, but few head-to-head prospective studies have been done to compare the effectiveness of various antifungal drugs for this purpose.
Empirical antifungal therapy typically is given to patients with neutropenia and fever that persists after 3–7 days of treatment with broad-spectrum antibiotics. Among the drugs commonly used for single-agent empirical therapy are lipid formulations of amphotericin B, echinocandins such as caspofungin, or triazoles such as voriconazole; all of these drugs work against a variety of fungal infections.

Dr. Kontoyiannis said that the selection of agents for primary antifungal therapy is determined by patient-specific characteristics—including the type, location, and severity of the infection; potential for organ toxicity; and possible drug-drug interactions. “The earlier you start therapy for fungal disease, the better the outcome,” he said.

Echinocandins are the main primary therapy for invasive candidiasis, but patients previously treated with azoles or echinocandins may be given liposomal formulations of amphotericin B. Voriconazole is the drug of choice for invasive aspergillosis, although lipid amphotericin B has been used with success. Combinations of voriconazole and other drugs have been studied as primary treatments for invasive aspergillosis, but the data do not support the wide use of combination treatment.

Dr. Kontoyiannis said the decision to use combination treatment should be made on a case-by-case basis.

Should the primary antifungal treatment fail, patient characteristics and prior treatments affect the choice of drugs for salvage therapy. Fungal lesions in the lungs that have not responded to antifungal drugs may be removed surgically if the number of lesions and their locations are amenable. Dr. Kontoyiannis said surgery is considered for selected patients with a good performance status who have not yet undergone stem cell transplantation.

Future directions

Although treatments for invasive fungal infections have improved in the past decade, researchers face obstacles in developing new antifungal drugs. “Fungi and humans are both eukaryotic organisms, which makes it difficult to find a cellular target that can be destroyed without collateral damage to the host,” Dr. Kontoyiannis said. “Not surprisingly, the pipeline for antifungal drug development is currently essentially empty, as pharmaceutical companies are staying away from that relatively small market. Therefore, wise and expert management of our current antifungal armamentarium—with a logical use of antifungals for different indications and in the context of formal guidelines and an antifungal stewardship program—are important.”

Nevertheless, researchers continue to search for new ways to treat or prevent invasive fungal infections in patients with hematological malignancies. Javier Adachi, M.D., an associate professor in the Department of Infectious Diseases, along with Dr. Kontoyiannis and other colleagues, is in the planning stages of a clinical trial of intermittent echinocandin use as prophylaxis against fungal infection in patients with graft-versus-host disease following stem cell transplantation. Also, Issam Raad, M.D., chair of the Department of Infectious Diseases, and colleagues are planning a study of pharmaceutically improved versions of the triazole posaconazole as a treatment and prophylaxis in patients with hematological malignancies who are at high risk for fungal infections—including patients who have undergone stem cell transplantation.

Finally, immune-enhancing strategies such as the use of growth factors and/or white blood cell transfusions for the prevention and treatment of opportunistic fungal infections in immunocompromised patients remain an important area of investigation.

As researchers work to improve antifungal therapy, accurate early diagnosis and prompt treatment remain the keys to fighting invasive fungal infections in patients with hematological malignancies. “These are relatively uncommon infections that need to be managed in a large center by expert clinical mycologists,” Dr. Kontoyiannis said, “particularly when patients have chronic, complicated, or resistant infections.”

FOR MORE INFORMATION
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IN BRIEF

Beta-Blocker Use Associated With Higher Survival Rates in Lung Cancer Patients Receiving Radiation Therapy

Using beta-adrenergic receptor antagonists (beta-blockers) prolongs survival in patients with non–small cell lung cancer (NSCLC) undergoing definitive radiation therapy, findings from a study at The University of Texas MD Anderson Cancer Center suggest.

The analysis, led by Daniel Gomez, M.D., an assistant professor in the Department of Radiation Oncology, found that the incidental use of beta-blockers in this population was associated with longer distant metastasis–free, disease-free, and overall survival.

Of the 722 patients included in the retrospective study, 155 had received beta-blocker treatment during radiation therapy. About two-thirds of those patients received beta-blockers to treat hypertension, and most of the remaining third received them to treat coronary heart disease.

A univariate analysis comparing outcomes for patients who received beta-blockers with those who did not revealed that the use of beta-blockers was associated with longer distant metastasis–free, disease-free, and overall survival. After adjustment for age, Karnofsky performance score, disease stage, tumor histology, use of concurrent chemotherapy, radiation dose, gross tumor volume, hypertension, chronic obstructive pulmonary disease, and aspirin use, a multivariate analysis revealed that the use of beta-blockers was still associated with longer distant metastasis–free, disease-free, and overall survival.

Several factors other than beta-blocker use also were significantly associated with survival. Concurrent chemotherapy was associated with longer overall survival; age younger than 65 years was associated with longer disease-free survival; a Karnofsky score greater than 80 was associated with longer distant metastasis–free survival, disease-free survival, and overall survival; and stage III disease was associated with shorter distant metastasis–free survival, disease-free survival, and overall survival.

The study was reported in *Annals of Oncology* in January. Dr. Gomez and his co-authors recommended prospective trials to determine whether the length and timing of beta-blocker use influence survival for cancer patients.

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Selumetinib Shows Promise for Patients With Recurrent Low-Grade Ovarian Cancer

Selumetinib, a MEK1/2 inhibitor, benefits some patients with recurrent low-grade serous ovarian cancer, according to the results of a recent phase II clinical trial.

The open-label, single-arm study—the first to evaluate targeted therapy for low-grade serous ovarian cancer—enrolled 52 patients with recurrent disease who had undergone at least one prior therapy. Patients were given 50 mg of oral selumetinib twice daily for a median of 4.5 4-week cycles; individual patients’ doses were adjusted on the basis of the hematological, dermatological, and/or gastrointestinal adverse events they experienced.

Selumetinib elicited a complete or partial response in 8 patients (15%) and stabilized disease for at least 6 months in 34 patients (65%). The median progression-free survival duration was 11 months, and the 2-year overall survival rate was 55%. There were no treatment-related deaths.

“These are remarkably encouraging results for what can ultimately be a devastating disease,” said David Gershenson, M.D., a professor in the Department of Gynecological Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center and the senior author of the study’s report.

The grade 4 adverse events experienced in the study were pain (1 patient) and cardiac and pulmonary events (1 patient each). Grade 3 adverse events included cardiotoxicity, gastrointestinal events, pain, fatigue, and anemia. Owing to these adverse events, the selumetinib dose was reduced in 22 patients, and 13 patients ultimately left the study.

Although low-grade serous ovarian cancer is less aggressive than its high-grade counterpart, it is extremely difficult to treat if initial therapy fails—and the cancer will persist or recur in more than 80% of patients. Recurrent or relapsed low-grade serous ovarian cancer is less susceptible to standard therapies than is high-grade disease, and response rates for recurrent or relapsed low-grade disease are usually below 10%.

“After surgery with or without presurgical chemotherapy, when low-grade serous ovarian cancer persists or returns, chemotherapy and hormonal therapy are relatively ineffective,” Dr. Gershenson said.

Selumetinib inhibits MEK1/2, a critical molecule in the MAPK signaling pathway, which includes BRAF and KRAS. BRAF and KRAS mutations are common in low-grade serous ovarian cancers. In the study, 14 patients had KRAS mutations, and 2 had BRAF mutations; but a patient’s having either mutation was not connected to her selumetinib response.

The study was conducted by the National Cancer Institute’s Gynecologic Oncology Group, and the report was published in the February edition of *The Lancet Oncology*.

[Continued on page 8]
Myths and Facts About Skin Cancer

What you don’t know could hurt you

Whether you’ve never been sunburned or you sunbathe regularly, you may think that you don’t need to worry about protecting yourself from the sun. But skin cancer doesn’t discriminate by age, race, or lifestyle—it can affect anyone. The first step in protecting yourself against skin cancer is to separate the myths from the facts.

**MYTH: Dark skin protects against skin cancer.**
**FACT:** Naturally darker skin doesn’t prevent skin cancer. Although skin cancer is less common in African American and Hispanic populations than in Caucasian populations, African American and Hispanic people who develop melanoma (an aggressive type of skin cancer) are more likely to die from the disease than are Caucasian people with melanoma.

The most likely reason for this difference in patients’ outcomes is that dark-skinned people are less likely to seek treatment for skin lesions before the disease has reached an advanced stage. For example, acral lentiginous melanoma, the most common melanoma in African Americans and Asians, often goes unrecognized because it affects parts of the skin where cancer is not expected, such as the palms, soles, and nail beds.

**MYTH: Tans are healthy and shield the skin from damage.**
**FACT:** A “base tan” may delay sunburn, but it will not prevent damage from ultraviolet radiation. In fact, tanning is the body’s attempt to defend itself against previous exposure to ultraviolet radiation by increasing the amount of pigment in the skin. This means that the DNA in suntanned skin has already been damaged by ultraviolet radiation. This DNA damage can lead to mutations that cause cancer. Also, a substantial amount of ultraviolet radiation will still penetrate any tan.

Whether caused by sunlight, a tanning bed, or a sun lamp, no tan leaves your skin healthier than it was before. Some tanning salons claim to use “safer” rays than those from the sun, which usually means ultraviolet A but not ultraviolet B rays. However, both types of ultraviolet rays can cause skin cancer.

**MYTH: Skin cancer develops only on parts of the body that have gotten too much sun.**
**FACT:** Although skin cancer most often occurs in areas that are frequently exposed to direct sunlight, cancer can also develop on skin that is usually covered by clothes or in shadow.

Because cancer can occur anywhere on the skin, a doctor performing skin cancer screening examines all areas of the skin. If you notice unusual spots or changes to existing moles anywhere on your skin or if you have multiple risk factors for skin cancer, talk to your doctor about skin cancer screening.

**MYTH: Only elderly people develop skin cancer.**
**FACT:** Skin cancer doesn’t happen only to older people. The two most common types of skin cancer, basal cell carcinoma and squamous cell carcinoma, do occur mostly in people more than 40 years old because these cancers are linked to a person’s built-up exposure to ultraviolet radiation over many years. Melanoma, however, is linked to the sudden damage caused by sunburn and thus is more likely in young adults than other skin cancers. In fact, according to the Skin Cancer Foundation, melanoma is the second most common of all types of cancer in people 15–29 years old and the most common cancer in those 25–29 years old.

**MYTH: Only people who don’t use sunscreen and spend too much time in the sun get skin cancer.**
**FACT:** Even though limiting your sun exposure can reduce your risk of getting skin cancer, the risk is not reduced to zero. Genes also influence the risk of developing skin cancer. So someone who wears sunscreen conscientiously but has a family history of skin cancer might develop the disease.

The risk of skin cancer can remain high for some people who use sunscreen because they are not using it properly. You should apply sunscreen (SPF 30 or higher) half an hour before sun exposure so it has time to penetrate the skin, and you should reapply sunscreen regularly, especially after swimming.

Even people who avoid outdoor activities are at risk for skin cancer because they too are exposed to ultraviolet radiation. People get most of their ultraviolet radiation exposure through routine activities like walking a dog or trying to find a parked car. Avoiding sunlight when it is strongest—between 10 a.m. and 4 p.m.—can reduce your exposure, as can wearing a hat and long sleeves during routine activities.

Knowing the facts and taking sensible precautions can help protect you and your family against skin cancer.

— S. Bronson

**FOR MORE INFORMATION**
- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
- Visit the Skin Cancer Foundation at http://www.skincancer.org/skin-cancer-information/skin-cancer-facts
Varenicline Improves Smokers’ Chances of Stopping Smoking

Smokers in a smoking cessation study who took varenicline had a higher probability of quitting smoking and a better overall cessation experience than did those who took bupropion or placebo, a team of researchers at The University of Texas MD Anderson Cancer Center has reported.

The team, led by Paul Cinciripini, Ph.D., a professor in the Department of Behavioral Science and the director of the Tobacco Treatment Program at MD Anderson, investigated the relative efficacy of varenicline and bupropion, two popular smoking cessation drugs, in nearly 300 people who were trying to quit smoking. Participants were randomly assigned to receive varenicline, bupropion, or placebo; they also underwent extensive smoking cessation counseling. Participants were assessed for nicotine withdrawal and emotional functioning every week during treatment.

The researchers found that, compared with placebo, only varenicline significantly improved smoking abstinence rates by all measures at all time points—a finding that is consistent with the results of phase III clinical trials of varenicline. Compared with placebo, both varenicline and bupropion reduced participants’ nicotine cravings, but people taking varenicline had less intense cravings for nicotine, even if they did not quit smoking.

“When smokers try to quit, many are likely to experience a range of nicotine withdrawal symptoms—including negative mood, difficulty concentrating, irritability, and even depressive symptoms—making quitting difficult and increasing the chances of relapse,” Dr. Cinciripini said. “Our findings suggest that smokers trying to quit will have a better experience with varenicline as opposed to trying to quit on their own or taking bupropion.”

Dr. Cinciripini and his colleagues also found that regardless of whether varenicline or bupropion was received, people who were able to abstain from smoking not only showed lower negative affect, less anxiety, and less sadness but also showed higher positive affect than those who were not able to abstain from smoking.

“This is a very interesting finding in that it suggests smoking itself may not be a very good antidepressant,” Dr. Cinciripini said. “It also suggests that those who are able to abstain from smoking will ultimately feel better than those who continue to smoke.”

The study was published online by JAMA Psychiatry in March.