Addressing the Cardiac Complications of Cancer Treatment

By Stephanie Deming

Patients with cancer are surviving longer than ever after treatment, and new targeted therapy agents are being introduced into the clinic with increasing frequency. These advances are cause for optimism, but they have also led to an increased incidence of cardiac complications of cancer therapy.

As with any complication of cancer therapy, clinicians seek to avoid cardiac complications if possible and to detect and treat any complications early to minimize their impact on patients' lives. Researchers at The University of Texas MD Anderson Cancer Center are working to develop improved methods for early detection of heart problems and for prediction of which patients are at highest risk for cardiac complications of anticancer therapy.

Heart failure: the most dreaded cardiac complication

According to Edward Yeh, M.D., chair of and a professor in the Department of Cardiology at MD Anderson, there are six major types of cardiovascular complications of cancer therapy:

- left ventricular dysfunction, the final manifestation of which is heart failure;
- ischemia;
- hypertension;
- thromboembolism;
- heart rate acceleration;
- hyperviscosity.

Heart failure is the most feared complication of cancer therapy because it can rapidly lead to death. Patients with cancer are more likely to experience heart failure than patients with heart disease. This suggests that the type of cancer treatment may be causing damage to the heart rather than the cancer itself. It is important to identify patients at risk for heart failure early and to treat them aggressively to improve their survival.

Compass:

Early- and Intermediate-Stage Gastric Cancer

Neoadjuvant or adjuvant treatments improve outcomes for many patients

House Call

Understanding the causes of fatigue may help patients decrease its severity
Anticancer drugs

Many anticancer drugs can cause left ventricular dysfunction, but the most problematic drugs are the anthracyclines, particularly doxorubicin. Anthracyclines have been in use for more than 40 years, and they are the most common cause of cardiac complications in cancer patients. Anthracyclines cause heart failure by directly damaging the heart muscle, and the risk of heart failure increases as the cumulative dose increases.

Trastuzumab, a monoclonal antibody that targets the HER2 cell surface receptor, and some other targeted therapies—including bevacizumab, dasatinib, imatinib mesylate, and sunitinib—may also cause left ventricular dysfunction.

According to Dr. Yeh, trastuzumab by itself does not usually cause heart problems. However, the combination of trastuzumab and doxorubicin can cause heart problems owing to a phenomenon called sequential stress. “If you already have underlying cardiac damage from the doxorubicin, and then you impose another stress in the form of trastuzumab, that can cause a problem,” he said. “The reason is that trastuzumab binds to a cardiac surface receptor called HER2 that is important for cardiac cells to survive. If you have damaged cardiomyocytes from doxorubicin treatment and then you block those prosurvival signals with trastuzumab, you can get into big trouble.”

The problem with sunitinib and some other targeted therapies is that the cancer-causing pathways they block may also be important for the survival of heart cells. “Sunitinib kills cancer cells by blocking the formation of blood vessels,” Dr. Yeh said. “So this drug can deprive cancer cells of their blood supply, but it also may cause harm to the heart.” A recent study also found that sunitinib blocks the heart cells’ response to stress. This is important because another possible side effect of sunitinib is hypertension.

Minimizing heart failure risk

Given the potential for heart failure due to anticancer therapy, oncologists generally screen patients before and during potentially cardiotoxic therapy to make sure that the heart is healthy enough to withstand treatment. The pretreatment screening includes a history to determine whether the patient has risk factors for therapy-induced heart damage, such as high blood pressure, high cholesterol, diabetes mellitus, or a history of smoking, heart disease, anthracycline therapy, or radiation therapy that included the left side of the chest. Echocardiography is performed to determine the left ventricular ejection fraction.

On the basis of this screening, the oncologist decides what type of therapy should be avoided, and this information is considered when deciding whether the patient is eligible to participate in a clinical trial or should receive the standard of care. “We have to personalize therapy,” said Apostolia M. Tsimberidou, M.D., Ph.D., an associate professor in the Department of Investigational Cancer Therapeutics, which conducts phase I clinical trials. “The type of therapy has to be carefully selected on the basis of the tumor characteristics and the patient’s history and characteristics, including risk factors for heart disease.”

Patients who have had a myocardial infarction within the preceding 6 months may be able to receive therapy with agents not associated with cardiotoxicity; however, these patients are usually excluded from participation in clinical trials. Most other patients are eligible to participate in clinical trials with anticancer therapy.

“Patients with a history of heart disease should avoid the use of potentially cardiotoxic drugs,” Dr. Tsimberidou said. “Patients who are treated with potentially cardiotoxic drugs—especially anti–vascular endothelial growth factor agents such as bevacizumab, sorafenib, and particularly sunitinib—should be followed closely with blood pressure monitoring and echocardiography.” More recently, levels of troponin I, a marker with almost absolute cardiac specificity and high sensitivity to cardiac damage, together with B-type natriuretic peptide have been used to monitor patients treated with potentially cardiotoxic drugs.

Dr. Tsimberidou added that because of the potential development of heart failure in some patients treated with sunitinib, physicians should suspect this complication when these patients develop fatigue or other symptoms suggesting heart failure. In such cases, physicians should withhold sunitinib until completion of a cardiac workup. If heart failure is proven, sunitinib should be discontinued. “This applies to patients participating in clinical trials and those treated in the community,” she said.

However, with trastuzumab, if screening shows a drop in the left ventricular ejection fraction, the next steps in therapeutic management are to stop trastuzumab; give a drug or drugs used to treat heart failure, such as an angiotensin-converting enzyme.
inhibitor or the combination of an angiotensin II receptor blocker and a beta-blocker; wait until heart function improves; and then consider starting trastuzumab again.

“Heart failure is heart failure, whether the damage results from a heart attack or from anticancer therapy,” said Dr. Yeh. In general, he said, the drugs used to treat heart failure in patients without cancer work equally well in patients with a drop in left ventricular ejection fraction due to anticancer therapy. The catch, though, is that therapy-induced heart failure has to be detected fairly early (i.e., within a couple of months) for heart failure treatment to be effective. In addition, some kinds of anticancer therapy—induced heart failure, such as heart failure caused by doxorubicin, generally are not reversible.

If the original anticancer therapy cannot be resumed, a switch to a non-cardiotoxic agent may be possible. Treating patients with cancer and heart disease is a balancing act, said Dr. Tsimberidou. “We should always think about the cost-benefit ratio,” she said. “If a patient is at high risk of dying from heart disease and the patient’s cancer is in remission, the physician should optimize the patient’s risk factors for heart disease and his or her cardiovascular medication, hold anticancer therapy, and monitor the patient’s cancer with imaging studies and tumor markers as applicable.”

Another issue that should be considered is how long treatment for anticancer therapy-induced heart failure needs to be continued. If a patient had heart failure, was successfully treated for that, resumed anticancer therapy (e.g., with trastuzumab), and is now finished with anticancer therapy, can the heart failure therapy be stopped? “The short answer to that is no,” Dr. Yeh said. “You should probably continue the heart failure therapy for some time after the completion of anticancer therapy, although that period has not been defined.”

Better screening on the horizon

Unfortunately, according to Dr. Yeh, ejection fraction as determined by either echocardiography or nuclear imaging is an imperfect measurement because it does not reveal abnormal left ventricular function until after substantial cardiac damage has occurred. The Department of Cardiology at MD Anderson has been investigating a number of alternatives that may allow earlier detection of cardiac damage from anticancer therapy and earlier intervention to limit or reverse this damage.

One alternative already in use is to measure the amount of the cardiac enzyme troponin I in the blood. Troponin I is released by damaged heart muscle cells, and measurement of troponin I is used in the diagnosis and monitoring of patients with myocardial infarctions. In patients with cardiac damage due to anticancer therapy, the level of troponin I increases before the ejection fraction decreases. “This test is not in wide use right now,” Dr. Yeh said, “but I think it has a lot of potential.”

Another potentially promising approach uses specialized echocardiography techniques to determine left ventricular strain, which is a measurement of how much each segment of the heart muscle deforms with each contraction. Strain usually becomes abnormal before left ventricular ejection fraction does. “We are routinely doing this now in our lab, and we are the only cancer center that does it,” said Dr. Yeh. “We are doing a larger-scale study to prove that this is indeed useful in our patients.”

Dr. Yeh and his group are also pursuing “a very clear lead” indicating that it may be possible to identify through a blood test patients who have a genetic predisposition to cardiac damage caused by certain types of anticancer therapy.

As anticancer therapy becomes more personalized, the assessment and treatment of cardiac complications should also become personalized. “We have created a new field called onco-cardiology,” Dr. Yeh said. “Our goal is to foment a close collaboration between cardiologists and oncologists so that our patients will have healthy hearts to enjoy their new lives.”

The Heart Success Program

For patients at MD Anderson who are diagnosed with anticancer therapy-induced heart failure, help is available in the form of the Heart Success Program, which includes a support group and patient education materials. Aneita Fadlo, Ph.D., an advanced practice nurse in the Department of Cardiology, helped develop the program. She explained how the program got its name: “We used to send patients e-mails and letters saying ‘You are invited to a heart failure support group.’ A patient’s wife pointed out that heart failure is really depressing. So we decided to change the name to something that is positive and is not depressing for patients. What is the opposite of failure? Success.” The patient education materials, which are available in both book and on-demand video format, explain heart failure and its symptoms, describe medications used to treat heart failure, and outline strategies for diet and lifestyle modifications to support heart health.

More information about the Heart Success Program is available at www.mdanderson.org/cardiology.
Early- and Intermediate-Stage Gastric Cancer

Neoadjuvant or adjuvant treatments offer higher cure rates than surgery alone

By Sunni Hosemann

Overview

This discussion addresses early- and intermediate-stage gastric adenocarcinomas—those that have not metastasized and are considered surgically resectable.

Most adenocarcinomas arise in the mucosal layer of the stomach; however, very few gastric cancers are diagnosed while still confined to the gastric mucosa (T1a tumors). Most gastric cancers are not discovered until they are more advanced.

Surgery is the definitive treatment for early- and intermediate-stage gastric cancers that have not metastasized. In most patients, however, surgery alone is considered insufficient. Chemotherapy and radiation therapy have both been shown to prolong survival in patients who undergo surgery for these tumors, but when these treatments should be done and in what order has yet to be defined by large randomized trials.

Traditionally, surgery has been the initial treatment for gastric cancers, and until recently, staging was not considered complete until the tumor was surgically removed and subjected to pathological analysis. However, gastric cancers are often found to be more advanced at surgery than initially thought. Also, because occult metastases are common in patients with gastric cancer, the disease may advance—particularly in the peritoneum—despite an R0 resection (the removal of the tumor with clear pathological margins). For these reasons, MD Anderson physicians believe that pretreatment staging is crucial to planning and implementing effective treatment.

Preoperative evaluation

A gastric tumor is considered resectable if there is no evidence of metastasis to the viscera or peritoneum as determined by a thorough preoperative workup. At MD Anderson, this workup includes preoperative staging of the tumor by endoscopic evaluation of the stomach, including ultrasonography, and a laparoscopic evaluation of the abdomen. “While important, imaging studies are inadequate for full staging of gastric cancer,” said Keith Fournier, M.D., an assistant professor in the Department of Surgical Oncology, who added that as many as 40% of gastric tumors may go undetected by positron emission tomography.

During the diagnostic laparoscopy, peritoneal washings are obtained for cytological analysis. “About 20% of the time, evidence of metastasis is found in the peritoneal washings, even in patients who don’t have observable metastases,” Dr. Fournier said. “Unfortunately, those laparoscopic findings have the same significance as visible metastatic

About Gastric Cancer

Gastric cancer is the fourth most common cancer in the world and the second leading cause of cancer-related deaths. According to recent estimates by the World Health Organization, more than 900,000 new cases of gastric cancer—and more than 740,000 deaths related to the disease—occur each year, with the highest incidence in the Western Pacific Region countries, notably Japan. Although the incidence of gastric cancer has declined over past decades in the United States, it remains one of the deadliest cancers in the nation. According to the most recent National Cancer Institute estimates, some 21,000 Americans will be diagnosed with stomach cancer in the coming year, and more than 10,000 are expected to die of the disease. The current 5-year overall survival rate for patients with very early-stage (T1) gastric cancers is estimated to be 71%. Unfortunately, most gastric cancers are not discovered until they are more advanced; the 5-year overall survival rate for patients with gastric cancer of any stage is about 28%.
### GASTRIC CANCERS: Standard Options for Early and Intermediate Stages

**Diagnosis:**

- **Gastric Cancer Stage I**
  - T1a
- **Gastric Cancer Stage II or III**
  - Potentially resectable T1b–T3, M0

### PRIMARY TREATMENT

- **Variables Considered for Each Patient**
  - Stage determined preoperatively
  - Performance status
  - Referral to experienced center possible?

- **Outcome-Based, Standard Treatment Options**
  - Surgery
  - OR
  - Endoscopic mucosal resection (EMR)

### ADJUVANT TREATMENT

- **Variables Considered for Each Patient**
  - R status
  - Performance status

- **Options for Adjuvant Treatment**
  - Observation
  - OR
  - Chemotherapy
  - Chemoradiation

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Lesions—they indicate stage IV disease, which is not considered resectable." Peritoneal washings may be repeated to re-stage the patient's disease after the patient has undergone treatment with chemotherapy or chemoradiation. Surgery may be reconsidered in very select patients who have no other evidence of metastatic disease and whose washings show no metastases after chemotherapy.

Also during the diagnostic laparoscopy, a feeding tube may be placed in the jejunum to maintain the patient's nutritional status if the patient is expected to undergo a course of neoadjuvant therapy.

### Treatment options

**Endoscopic mucosal resection**

According to Jeffrey H. Lee, M.D., a professor in the Department of Gastroenterology, Hepatology and Nutrition, preoperative tumor staging by endoscopic ultrasonography, which can show the degree of tumor invasion in the very fine layers of the stomach wall, can help determine whether a patient should undergo gastrectomy or endoscopic mucosal resection (EMR). EMR is a minimally invasive operation that is usually done as an outpatient procedure and can be repeated if necessary. Patients with T1a gastric cancers are candidates for EMR.

In EMR, an indigo-colored saline solution is injected between the mucosa and submucosa of the stomach to separate these layers—in effect, the submucosa is ballooned away from the mucosa so that tumor-bearing tissue may be carefully resected. A suction mechanism on the endoscope is used to lift the tumor, which is captured by a snare and excised.

Because each of the tissue layers is only millimeters thick, the surgery is very intricate work; the obvious potential complication is a perforation of the stomach wall.

EMR for gastric cancers differs notably from that performed relatively routinely for other gastrointestinal lesions, such as polypoid lesions of the colon. Adenocarcinomas of the gastric lining tend to be flatter than polypoid lesions and are thus more difficult to snare. As a result, EMR for gastric tumors is a very specialized procedure that is not widely available outside comprehensive cancer centers.

**Surgical resection**

Surgery—either total or subtotal gastrectomy—is the definitive curative treatment for patients with T1a tumors who do not have access to EMR and for patients with resectable T1b–T3 tumors. The surgery is a traditional open procedure, the goal of which is to achieve an R0 resection, Dr. Fournier said.

In addition to the tumor, regional lymph nodes are resected at the time of surgery. According to Dr. Fournier, an extended (D2) lymphadenectomy is recommended, which includes perigastric (D1) nodes as well as nodes adjacent to vessels such as the left gastric, hepatic, and splenic arteries. “A D1 resection is probably not sufficient,” Dr. Fournier said, “and D3 resections, which include a splenectomy, are associated with increased morbidity and...”
mortality and have not been shown to improve survival in Western patients, so they are not usually considered necessary.” He said that at least 15 lymph nodes should be removed for examination.

Tumor size and location affect the extent of surgery. Tumors in the antrum are often amenable to subtotal gastrectomy, whereas tumors in the proximal stomach and larger tumors may require more extensive surgery. According to Dr. Fournier, total gastrectomy is done only if necessary to achieve adequate clear margins—beyond that goal, total gastrectomy has no oncological advantage.

**Chemotherapy and radiation therapy**

Given the aggressive behavior of gastric tumors and the fact that occult disease has been identified in a significant number of patients with these tumors, additional therapy—chemotherapy or chemoradiation—is strongly considered for patients with T1b–T3 tumors.

“Surgery alone is insufficient treatment in most patients with localized gastric cancer,” said Jaffer Ajani, M.D., a professor in the Department of Gastrointestinal Medical Oncology.

Studies have shown that the addition of neoadjuvant and/or adjuvant therapy to surgery offers higher cure rates than does surgery alone. Improvements have been documented in overall and disease-free survival durations with each of the two approaches. However, each therapy has potentially serious side effects and toxicities.

Two neoadjuvant chemotherapy regimens commonly used with radiation therapy for adenocarcinoma are modified epirubicin, cisplatin, and 5-fluorouracil and modified docetaxel, cisplatin, and 5-fluorouracil. Only fluoropyrimidines are recommended with radiation therapy in the adjuvant setting. The choice of a certain combination and schedule depends on multiple variables, including the patient’s overall condition and nutritional status.

**Treatment sequence**

There are numerous options for sequencing treatment modalities. Preoperative chemotherapy may be given by itself or as induction therapy followed by chemoradiation therapy. Chemotherapy also may be given postoperatively, with or without radiation therapy.

No large randomized trials have directly compared preoperative treatments to postoperative treatments; however, preoperative treatment is preferred at MD Anderson. “In our experience, the efficacy of additional treatment is similar whether given pre- or postoperatively, but preoperative treatment is better tolerated,” Dr. Ajani said.

According to Pratijn Das, M.D., an associate professor in the Department of Radiation Oncology, therapy for gastric tumors can be delivered more accurately before surgery than after. “We know exactly where the tumor is,” he said, “so we can design the radiation field with greater precision.”

He added that the radiation field can sometimes be smaller before surgery than after. This, along with the fact that some irradiated tissue is subsequently removed during surgery, means that less tissue is exposed to radiation, with a concomitant reduction in side effects. In addition, when radiation therapy is given after all or part of the stomach has been resected, adjacent organs and tissues like the small bowel fall into the radiation field, which increases these tissues’ vulnerability to radiation damage.

Radiation therapy may also be more effective when given preoperatively because the blood supply is intact and the tissue is oxygenated.

Dr. Fournier said that preoperative chemotherapy treats lymph nodes, which often become involved early in gastric cancer. In addition, he said that preoperative treatment may help to “sterilize” the surgical field of cancer cells so that fewer cancer cells are shed into the abdomen during surgery. The ability to observe tumor response to treatment is another advantage of neoadjuvant therapy over adjuvant-only therapy.

Because the multimodality treatments necessary to achieve a cure are rigorous, perhaps the most compelling reason to favor preoperative therapy is that it is easier to tolerate than postoperative therapy. Thus, patients are more likely to receive the complete course of recommended treatments. “Among patients who only receive adjuvant treatments, approximately 30% drop out before finishing because of symptoms they find intolerable,” Dr. Fournier said.

Adjuvant treatments are recommended for patients whose disease is found to be more advanced than presurgical staging indicated, patients referred after surgery has already been done, and patients whose postoperative pathological analysis...
Managing Disease-Related Fatigue
Patients and doctors often can make fatigue less severe

Feeling tired during a long illness seems normal.
The idea of illness is closely tied to the image of someone lying in bed, and fatigue occurs with many chronic diseases. However, overwhelming fatigue is not something a patient simply has to accept. In fact, fatigue related to chronic illness is likely to improve with mindful treatment.

When fatigue is not normal
How do you know when to ask for help when dealing with fatigue? “The key is interference with functioning,” explained Carmen Escalante, M.D., chair of and a professor in the Department of General Internal Medicine at The University of Texas MD Anderson Cancer Center. If you persistently have trouble doing everyday tasks because you are too tired, or if rest and sleep no longer seem to restore your energy, you are probably experiencing severe fatigue and should seek help. Fatigue may go unreported because its nature varies from situation to situation. For example, many people associate fatigue with physical exhaustion, but fatigue can also show itself as depression or the inability to concentrate. In fact, a lack of energy can decrease your ability to function physically, mentally, or emotionally. Fatigue can be particularly hard to manage as a symptom of a chronic illness such as cancer, multiple sclerosis, muscular dystrophy, gastric disease, or thyroid disease. Some gastric diseases can prevent the absorption of food, diminishing available energy. Some diseases of the blood can reduce circulating oxygen, making physical activities more difficult to perform. For people with cancer, fatigue often becomes more distressing after aggressive treatments such as radiation therapy and chemotherapy.

Managing fatigue
Dr. Escalante said that managing fatigue related to chronic disease requires a comprehensive approach. Because fatigue is multidimensional, its exact cause can be hard to pinpoint and treat. Pain, lack of nutrition, infection, dehydration, stress, depression, anxiety, or hormone imbalances may contribute to fatigue. Many patients with chronic diseases have multiple health problems that may affect fatigue and its management. Therefore, according to Dr. Escalante, the first step of controlling fatigue is seeking out all potential causes rather than viewing fatigue as an independent problem.

Fatigue related to chronic disease can often be managed by adjusting your habits. Dr. Escalante said that one of the most effective strategies for fighting fatigue is exercise. Severely fatigued patients tend to think that they need more bed rest, as they would with normal physical fatigue, but sometimes the opposite is true: Evidence shows that simple exercise can be one of the most powerful ways to fight fatigue. Even a light regimen of about 2½ hours of exercise spaced throughout the week can raise your energy level.

However, too much exertion can be dangerous with conditions like recent surgery, bone metastases, or immunosuppression. Your physician can help you determine the level of exercise that’s right for you. Physical therapy may be more appropriate for some patients.

Mental activity also may reduce fatigue, especially if your condition prevents physical activity. You can engage your mind with a puzzle, a craft, or a good book. A controlled sleep schedule also can help restore energy. Going to bed at the same time every night and getting out of bed at the same time every day may reduce sleep problems. Cognitive behavioral therapy, which helps patients address negative thoughts that affect behavior, has also been shown to improve symptoms of chronic fatigue.

You might ask your doctor whether you should try a new drug regimen. Some medications have the potential to cause fatigue, and in some cases a different medication may serve the same purpose without the side effect. In addition, physicians sometimes prescribe psychostimulants to help patients gain more energy, especially patients who are adjusting to a new exercise routine or a more regular sleep schedule.

Misconceptions about fatigue
Although fatigue is a common symptom of many chronic diseases, some people are reluctant to seek treatment for it. Not everyone will think anything is wrong when fatigue accompanies a long illness. Some believe, mistakenly, that the best treatments for their disease will be withheld from them if they admit they are tired.

Another misconception is that fatigue means your disease is getting worse. In fact, cancer survivors sometimes continue to feel exhausted after they have been cured. Fatigue itself can affect how willing you are to do something about feelings of fatigue. Nevertheless, the majority of fatigued patients can be helped if they work with their health care provider to develop a fatigue management strategy.

—S. Bronson

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Compass

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indicates that an R0 resection was not achieved. However, these are less-than-ideal situations, underscoring the need for close multidisciplinary collaboration before treatment begins. According to Dr. Ajani, this collaboration should occur not as a series of sequential referrals and treatments but simultaneously in all planning and treatment phases; such teamwork almost always requires the infrastructure of a comprehensive cancer center. “Patients need this collaboration to have the maximum chance of a cure,” he said.

On the horizon

Researchers continue to seek better treatments for gastric cancer. One important development relates to the presence of the HER2 protein, which is found in 10% of gastric tumors. Dr Ajani explained that the HER2 protein triggers a signaling pathway that stimulates cancer cells to multiply. When trastuzumab, a monoclonal antibody that interferes with HER2 receptors, is used to block the signaling pathway, tumor growth is stopped. More important, cells susceptible to trastuzumab release a chemical “panic signal,” and the immune system responds with killer T cells. “Cancer cells that have managed to evade the immune system by appearing as ‘self’ are then recognized as non-self,” Dr. Ajani said. “And the immune system is able to kill the cell.”

Other tumor characteristics may soon enable physicians to identify which gastric cancer patients are likely to benefit from specific therapies, thanks in part to the research of Ju-Seog Lee, Ph.D., an assistant professor in the Department of Systems Biology, and his colleagues. Dr. Lee is analyzing tissue samples from gastric tumors to identify genomic signatures that could be used to guide treatment. Using tissue samples from collaborators at four institutions, Dr. Lee is mapping the samples’ genetic patterns of expression using an array of more than 300 genes. Eventually, he expects to identify 5–10 genes that would become the basis for testing biopsied tissue to identify patients whose tumors are likely to respond to radiation therapy and specific chemotherapy drugs. “This would occur before the patient is treated,” Dr. Lee said, “and would be a basis for individualizing treatment.”

Because he is able to collaborate directly with clinicians, Dr. Lee is optimistic about being able to translate this research to practice, which would give physicians another preoperative screening tool with which to tailor therapy for each patient.

References