OncoLog
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Treating Diabetes in Cancer Patients

By Zach Bohannan

Type 2 diabetes is a serious health concern for any patient—but when the patient also has cancer, diabetes may interfere with potentially life-saving cancer treatment.

Concurrent diabetes and cancer is relatively common because of the high prevalence of both conditions. However, researchers are only beginning to understand the interactions between diabetes and cancer. "There is a growing body of research on diabetes," said Sai-Ching "Jim" Yeung, M.D., Ph.D., an associate professor in the Department of Emergency Medicine at The University of Texas MD Anderson Cancer Center. "And now cancer researchers are beginning to integrate that knowledge into our understanding of how cancer develops and responds to treatments."

***Dr. Victor Lavis** discusses diabetes management with [redacted] (left) and her sister, [redacted] has diabetes and is undergoing testing for a potentially malignant neoplasm.*

Interactions

A potentially important interaction between diabetes and cancer is the common thread of insulin signaling. Insulin is a potent promoter of cell growth and may be implicated in the development of some common cancers. Insulin-like growth factor receptors are often mutated in cancers, and the resulting dysregulation of the insulin signaling system may lead to rampant proliferation in some types of cancer.

Hyperinsulinemia, which can result from the disruption of insulin signaling or production, is a risk factor for the development and progression of several cancer types, including prostate and breast cancers. In contrast, lower insulin levels have been associated with better outcomes in diabetic patients with prostate or breast cancer.

Diabetes caused by cancer

Although many patients have diabetes long before their cancer diagnosis, it is equally as common for patients to develop diabetes because of their cancer or its treatment.

Cancer-related diabetes is most often associated with pancreatic cancer. In fact, the onset of diabetes in an otherwise healthy elderly patient is a potential warning sign

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Dr. Victor Lavis *examines a patient's feet for signs of diabetes-related circulatory or neurological complications.*

of pancreatic cancer. Although it is currently not clear how diabetes and pancreatic cancer interact, their association is well documented.

Also linked to diabetes are tumors that secrete cytokines, especially those that secrete large amounts of interleukin-6. Although the role of cytokines in insulin signaling has yet to be fully characterized, interleukin-6 and other proinflammatory cytokines can cause insulin resistance. This resistance is possibly related to increased inflammatory signaling throughout the body.

Diabetes caused by cancer treatment

The most common cause of cancer treatment–induced diabetes is glucocorticoid therapy. According to Victor Lavis, M.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders, nearly half of the diabetic and insulin-resistant patients treated at MD Anderson are patients whose cancer treatments include glucocorticoids.

Glucocorticoids, which reduce inflammation and affect lymphocyte development, are often used as part of the treatment for hematological malignancies and some solid tumors. Glucocorticoids are also given to prevent or treat graft-versus-host disease in patients who have received allogeneic stem cell transplants for hematological malignancies (see *OncoLog*, April 2013). Furthermore, glucocorticoids are frequently prescribed by oncologists to control nausea or to reduce swelling in the central nervous system.

However, in addition to their beneficial effects, glucocorticoids reduce glucose clearance and disrupt the function and survival of insulin-secreting pancreatic beta cells. These disruptions to glucose metabolism cause insulin resistance and hyperglycemia and, over time, may lead to permanent diabetes.

Many cancer patients who are treated with glucocorticoids will eventually need some sort of medication for their hyperglycemia. However, Dr. Lavis said, the question of which diabetes medication would allow the best response to cancer therapy for patients with glucocorticoid-induced diabetes has yet to be explored in clinical trials.

> **"[C]ancer researchers are beginning to integrate that knowledge [from diabetes research] into our understanding of how cancer develops and responds to treatments."**
>
> **– Dr. Jim Yeung**

Prevalence of Diabetes and Cancer

The U.S. Centers for Disease Control and Prevention estimates that **25.8 million people in the United States, or 8.3% of the population, have diabetes.**

The American Cancer Society estimates that **12.5 million Americans have a history of some type of invasive cancer.**

Treating diabetic patients with cancer

Many diabetic cancer patients have poorly controlled blood sugar at the time of their cancer diagnoses. These patients' blood sugar must be brought under control before they can safely undergo cancer treatment.

Until recently, a patient's diabetes and cancer were treated as if they were unrelated. However, physicians are finding that some diabetes treatments seem to be more effective than others for controlling blood sugar in patients with concurrent cancer. Dr. Yeung said, "Evidence is mounting that metformin is superior to other common therapies for treating diabetes in cancer patients."

Metformin works by blocking liver gluconeogenesis rather than affecting the insulin signaling pathway. Insulin-based diabetes treatments tend to address the hyperglycemia by simply increasing insulin levels to overcome the patient's insulin resistance.

Future directions

Because of the increasing numbers of patients with cancer who enter the clinic with diabetes or who develop hyperglycemia during their treatment, the interaction between diabetes and cancer is becoming an important research topic. However, the field is still in its infancy. Although some studies have linked hyperglycemia and diabetes to cancer treatment outcomes, few mechanisms have been elucidated.

Furthermore, there are currently no standard guidelines for the treatment of diabetes in cancer patients. Metformin is preferred on the basis of experience and preliminary research, but it is currently unclear whether metformin is useful in all cases of concurrent diabetes and cancer. Much more research is needed. ■

FOR MORE INFORMATION

Dr. Victor Lavis.....713-792-2841
Dr. Jim Yeung.....713-745-9911

FURTHER READING

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IN BRIEF

MET Protein May Serve as a Biomarker for a Treatment-Resistant Colorectal Cancer Subtype

The MET protein may be a surrogate indicator of the presence of the chemotherapy-resistant epithelial-mesenchymal transition (EMT) subtype of colorectal cancer, a recent study showed.

EMT occurs when epithelial cells change shape and lose cell-to-cell adhesion molecules, thereby allowing the cells to adopt certain characteristics of mesenchymal cells, such as invasiveness and resistance to cell death.

Currently, the EMT subtype is identified by its genetic "signature"—multiple gene mutations. However, a single biomarker for this subtype has not been previously identified.

"While we know there are many types of colorectal cancer, we're not as advanced as we'd like to be in our understanding of them," said Scott Kopetz, M.D., Ph.D., an associate professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center. "One of the larger goals of our research is to find simple biomarkers that can be used by doctors in the community to identify subtypes. We want to condense sophisticated gene signatures down to single markers and simple tests that can be used to guide therapy."

> ***"We want to condense sophisticated gene signatures down to single markers and simple tests that can be used to guide therapy."***
>
> **– Dr. Scott Kopetz**

To determine whether MET protein could serve as a biomarker for EMT, Dr. Kopetz and his colleagues compared MET protein expression with the expression of proteins and messenger RNA for genes known to be altered in EMT. The researchers used data from The Cancer Genome Atlas to conduct an exploratory analysis of 139 untreated primary colorectal cancer samples.

Dr. Kopetz and his colleagues found that the expression of MET protein strongly correlated with the expression of the EMT-associated transcription factor Slug and of ERCC1, a marker for oxaliplatin resistance. High levels of MET protein expression also correlated with high expression levels of EMT-related genes. Higher levels of MET protein were associated with decreased overall survival durations. Colon tumors had higher levels of MET protein than rectal tumors did.

The results of this study may allow physicians to use MET protein expression as a biomarker for this often chemoresistant subtype of colorectal cancer. Dr. Kopetz and his colleagues presented their findings at the American Society of Clinical Oncology's annual meeting in June. ■

Compass

Quarterly discussion of cancer types for which there is no standard treatment or more than one standard treatment

Penile Cancer

Although curable, localized or regional squamous cell carcinoma of the penis presents treatment dilemmas

By Sunni Hosemann

Introduction

Squamous cell carcinoma (SCC) of the penis is treatable and curable when detected early. However, because the disease is rare, no large, randomized clinical trials of penile SCC have been conducted. For this reason, treatment recommendations for this cancer have been derived from small trials, from retrospective analyses, from what has been learned about similar cancers—vulvar, cervical, and head and neck SCCs—and from expert experience.

According to the National Cancer Institute, penile cancer accounts for less than 1% of cancers in men in the United States. More than half of penile cancers are diagnosed in men 60 years or older; however, 22% occur in men younger than 40 years.

Some factors are known to affect the incidence of penile cancer. According to Curtis Pettaway, M.D., a professor in the Department of Urology at The University of Texas MD Anderson Cancer Center, the incidence of penile cancer is highest among men not circumcised in childhood, men who develop phimosis, men with AIDS or other immune deficiency disorders, and men treated for psoriasis with ultraviolet light (alone or with psoralens) without genital protection during treatment. Another potential risk factor is human papillomavirus infection, which is suspected to play a role in about 40% of penile cancers.

Although melanomas and sarcomas can affect the penis, 95% of penile cancers are SCCs, and this discussion is confined to potentially curable SCCs, which include localized disease and disease that has metastasized to regional lymph nodes but not distant sites (any T, any N, M0).

The 5-year relative survival rate is 85% for men with SCC confined to the penis, 59% for men whose disease has spread to lymph nodes, and 11% for men whose disease has spread to distant sites.

Prognostic factors

Men with limited inguinal lymph node metastases are often cured with surgery alone, whereas men with bulkier inguinal metastases and pelvic metastases may be cured by surgery and chemotherapy. However, distant metastases from penile SCC are not curable and tend to be rapidly fatal.

These disparate prognoses are why surgical exploration for potential occult nodal disease is appropriate for some patients with no clinical evidence of inguinal spread (i.e., no palpable lymph nodes). However, inguinal lymph node dissection (ILND) is associated with significant morbidity. Physicians must therefore determine the risk of regional spread.

One determinant of risk for regionally advanced disease is the pathological makeup of the primary lesion. Less differentiated tumors and those with evidence of microvascular or lymphovascular invasion have an increased risk of metastasis to regional lymph nodes.

Disease evaluation

According to Dr. Pettaway, treatment decisions are heavily dependent on a thorough assessment of the extent of disease. This assessment begins with a clinical evaluation of the primary lesion and regional lymph nodes. The primary lesion must be clinically assessed for size, location, involvement of the scrotum or base of the penis, fixation, depth of invasion, and involvement of corporeal bodies (i.e., submucosa, urethra, corpora spongiosum or cavernosum). In addition, the lymph nodes in the groin are palpated for evidence of involvement, which is a strong prognostic indicator. In obese patients, whose lymph nodes are more difficult to palpate, imaging modalities such as computed tomography can provide useful staging information about the presence of inguinal or pelvic adenopathy.

The primary lesion must also be biopsied to determine the histological grade and the presence of vascular invasion. The likelihood of micrometastases is increased in patients whose primary tumor is poorly differentiated or found to exhibit lymphovascular invasion. Such tumors are categorized as T1b or greater according to the American Joint Committee on Cancer's TNM staging system. In patients with these tumors, regional lymph nodes should be assessed to determine whether regional metastases are present, even if there is no palpable lymphadenopathy. Such an assessment

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is usually accomplished by superficial ILND, dynamic sentinel node biopsy, or inguinal ultrasonography and biopsy.

Primary tumor treatment options

Penectomy or conservative measures?

The goal of treatment in patients with penile SCC is to eradicate the cancer with minimal impairment of organ function. "For this cancer, surgical resection remains the gold standard for the treatment of the primary tumor," Dr. Pettaway said. "However, the extent of resection necessary is a concern for both aesthetic and functional reasons, and organ-sparing options can be considered in select patients."

Partial or total penectomy often is necessary for tumors that require wide surgical excision, including tumors that are grade 3 or higher; tumors that are 4 cm or larger; tumors that have penetrated the glans, urethra, or corpus cavernosum; and tumors located on the penile shaft.

For Tis, Ta, and T1 tumors that have no nodal extension and a favorable histology (i.e., low grade and well differentiated with no vascular invasion), organ-sparing treatment options may include topical therapy, laser ablation, or limited surgical excision.

"The goal of these treatments is to remove the tumor while preserving glans sensation and retaining the maximum possible penile shaft length," Dr. Pettaway said. Fortunately, nearly 80% of SCCs present on the prepuce, on the glans, or in the coronal sulcus—distal locations that lend themselves to organ-conserving approaches.

However, these organ-conserving methods carry a higher risk for disease recurrence than penectomy does. Patients who undergo conservative procedures should be counseled about the need for increased self-examination and surveillance, as early detection increases the likelihood that a locally recurrent lesion also will be amenable to conservative treatment.

LOCALIZED OR REGIONAL PENILE SQUAMOUS CELL CARCINOMA: Treatment Options

DIAGNOSIS: Squamous Cell Carcinoma of the Penis (Any T, any N, M0)	*Variables Considered for Each Patient*	*Treatment Options*
Primary Tumor	• Tumor size, location • Tumor histology • Tumor stage, grade • Personal preference • Likely compliance with surveillance	**Topical or laser therapy** OR **Surgery** Limited excision, glansectomy, or partial or total penectomy OR **Radiation therapy ± concurrent chemotherapy**
Inguinal Lymph Nodes	• Risk based on primary lesion characteristics • Number of involved nodes • Bilateral or unilateral involvement • Likely compliance with surveillance	**Surveillance** OR **Surgery ± chemotherapy** Inguinal lymph node dissection ± pelvic lymph node dissection OR **Concurrent radiation therapy and chemotherapy**

Limited surgical excision

Low-grade T1a tumors located on the glans may be treated with limited excision of the glans or glansectomy, sparing the penile shaft; tumors confined to the prepuce may be treated with circumcision. Conservative surgery should be done in conjunction with intraoperative pathological analysis to ensure negative surgical margins.

Mohs micrographic surgery also offers the potential for functional and aesthetic preservation of the penis for patients with small, distal, low-grade, early-stage lesions. The Mohs procedure is an excisional treatment performed by dermatological surgeons in an outpatient setting. As with limited excisions performed by urologists, intraoperative pathological analysis is performed to confirm negative surgical margins.

Laser ablation

Laser ablation is most useful for superficial penile lesions. CO_2-based lasers have a very small depth of penetration and were commonly used in the past. But newer, high-energy, neodymium-doped yttrium aluminum garnet–based lasers have a deeper penetration capability, and the recent use of these lasers to ablate penile lesions has resulted in high rates of resumption of sexual activity and patient satisfaction. Like conservative surgery, laser ablation should be done in conjunction with frozen section tissue analysis to ensure adequate margins.

Topical therapy

Topical cream formulations of 5-fluorouracil or 5% imiquimod used daily or every other day for 4–6 weeks are options for patients with Tis penile lesions, especially those

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who are not good candidates for surgery. These agents achieve good functional and aesthetic results; however, many patients do not complete the recommended course of treatment because the agents irritate the skin.

Radiation therapy

Radiation therapy (brachytherapy or external beam radiation therapy) is a treatment option considered for men with T1b or T2 tumors when technically feasible. Radiation therapy can preserve the penis, but the high doses of radiation that are necessary to treat SCC can cause acute edema and desquamation as well as late urethral stricture or tissue necrosis. Penile preservation rates of 70%–90% have been reported in appropriately selected patients treated with brachytherapy.

Radiation therapy also may be used to treat T3 or greater tumors in patients who refuse or who are medically unable to tolerate surgery. For these patients, radiation is administered concurrently with chemotherapy. "There are limited data on outcomes after chemoradiation therapy for penile SCC," said Karen Hoffman, M.D., an assistant professor in the Department of Radiation Oncology. "However, definitive chemoradiation is a proven, effective therapy for other human papillomavirus–related SCCs, including cervical and anal SCC."

Regional lymph node treatment options

The spread of penile cancer from the penis to metastatic sites is orderly and virtually always occurs first in the inguinal lymph nodes. Thus, a plan for management of the inguinal region should be considered in the overall management plan when the cancer is first diagnosed.

Surgery, observation, or neoadjuvant therapy?

ILND can offer a cure in many patients whose penile SCC has metastasized to the inguinal lymph nodes. However, the procedure comes with significant drawbacks. Although improved surgical techniques and better perioperative care have reduced the incidence of complications from ILND, its associated morbidities can include wound infection and dehiscence, seromas, venous thromboembolic events, and chronic lymphedema of the scrotum and lower limbs. For these reasons, ILND can be controversial. Therefore, physicians must determine the best way to stage the inguinal nodal basin and stratify patients for treatment.

Surveillance is considered for patients who have no palpable lymph nodes and are considered to be at low risk (i.e., Tis, Ta, grade 1 T1) or intermediate risk (i.e., grade 2 T1 without lymphovascular invasion) for inguinal involvement. For all other patients, superficial ILND and dynamic sentinel node biopsy are the standard staging tools. The results of these studies then allow physicians to make decisions about the need for additional procedures.

Palpable inguinal lymph nodes require immediate investigation. Because 30%–50% of enlarged lymph nodes are caused by inflammation, patients in the past were given a 6-week course of antibiotics before further investigation of palpable lymph nodes, but this is no longer recommended. Even when antibiotics are administered for underlying cellulitis or inflammation, investigation of the lymph nodes should proceed immediately.

Superficial ILND with frozen section analysis (followed by complete ILND if necessary) is recommended for patients with mobile palpable nodes confined to one side of the groin. Fine needle aspiration cytology, while not sufficiently sensitive for complete inguinal staging, can provide information to help determine the next steps in treatment, especially in patients with bilateral nodal involvement or fixed palpable nodes.

Another method for staging the inguinal nodal basin is dynamic sentinel lymph node biopsy, in which a radioactive dye is injected near the tumor to visualize the draining (i.e., sentinel) inguinal nodes. Recent data suggest that dynamic sentinel lymph node biopsy may be less morbid than superficial ILND, but this finding requires further validation.

If cancer is found in the inguinal nodes, the next consideration is the pelvic nodes. "We never see pelvic involvement without inguinal disease," Dr. Pettaway said, "and distant disease is always in the setting of high-volume disease in the inguinal and pelvic nodes."

According to Dr. Pettaway, patients found during ILND to have two or more involved inguinal nodes, evidence of extension into extranodal tissue, or poorly differentiated histologies should undergo pelvic lymph node dissection. If pelvic disease is found prior to ILND, neoadjuvant chemotherapy should be considered.

Neoadjuvant therapy

According to Lance Pagliaro, M.D., a professor in the Department of Genitourinary Medical Oncology, men with metastases in three or fewer unilateral inguinal nodes and no pelvic nodal involvement who are treated with surgery alone have a disease recurrence rate of 10%–20%. But in patients who have bulky or bilateral inguinal nodal involvement, pelvic nodal involvement, or extension into extranodal tissue and who are treated with surgery alone, the recurrence rate is 80%–90%. Dr. Pagliaro said that in these patients, neoadjuvant chemotherapy, radiation therapy, or chemoradiation should be considered.

Neoadjuvant chemotherapy followed by consolidation surgery is the preferred treatment for patients who have regional disease involvement beyond two unilateral lymph nodes and are willing and able to undergo surgery. A prospective, nonrandomized phase II trial reported in 2010 by Drs. Pagliaro and Pettaway and their colleagues established the efficacy of neoadjuvant chemotherapy with paclitaxel, ifosfamide, and cisplatin in patients with SCC of the penis classified as any T, N2–3, M0.

"The results surprised us," Dr. Pagliaro said. "We found that 50% of the patients had a response to chemotherapy—that's more than we expected—and 37% of the patients

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Stand Up for Your Health

Prolonged sitting may increase your risk for cancer and other diseases

HOUSE•CALL PATIENT INFORMATION SHEET

You might want to stand up to hear this news. Researchers have found that frequent sitting for long periods of time is linked to multiple health problems. Too much sitting increases inflammation, insulin resistance, and weight gain.

Unfortunately, many people's work requires sitting at a desk for 8 hours each day—plus a long commute sitting in a car or bus. Watching television at home adds to the number of hours spent sitting.

Health risks from sitting

Sitting for long periods of time has been shown to increase the risks of heart disease, diabetes, and some cancers.

One study of men in the Netherlands reported that occupational sitting (6–8 hours per day) increased the risk for colon cancer. Other studies found that women who sat for long periods were also at a higher risk for developing endometrial cancer than were those who did not, regardless of whether the women participated in moderate to vigorous physical activity. A U.S. study found that women who sat for 6 hours or more per day had a 28% higher risk of non-Hodgkin lymphoma than did women who sat for less than 3 hours per day.

In fact, exercise alone does not counter the increased cancer risks of prolonged sitting. The American Cancer Society published a study in 2010 in which mortality rates during the 14-year follow-up period were lower for participants who exercised regularly than for those who did not. However, study participants who sat for 8 hours or more per day had higher mortality rates than those who sat for less than 3 hours. In other words, physical exercise seems to reduce but not eliminate the negative effects of sitting.

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Minimize your risk

Even if your work requires you to sit for long periods, there are steps you can take to protect your health. "Taking a 1- to 2-minute break from sitting every hour may help lower your cancer risk," said Karen Basen-Engquist, Ph.D., a professor in the Department of Behavioral Science and the director of the Center for Energy Balance in Cancer Prevention and Survivorship at The University of Texas MD Anderson Cancer Center. "That's because even short spurts of movement can help minimize insulin resistance and long-term weight gain—factors that make it harder for the body to fight off cancer."

To get in the habit of taking breaks, try setting alarms for every hour to remind yourself to stand up and stretch a bit, go for a short walk, or do other simple exercises. Smart phone applications can send these reminders and also help track your activity. Try standing up and pacing in the office if you have to make a phone call, or schedule walking meetings with coworkers.

Dr. Basen-Engquist suggested investing in a pedometer to track how much activity you fit into your day apart from time dedicated to exercise. Most experts recommend walking 10,000 steps per day, roughly equivalent to 5 miles.

Taking the stairs when possible, instead of an elevator or escalator, also may ward off the effects of prolonged sitting. "Taking the stairs gets your heart pumping, builds muscle, strengthens bones, and burns calories. And the more often you take the stairs, the bigger the payoff," Dr. Basen-Engquist said.

At home, it's important to avoid sitting in front of the television or computer for long periods. If you do watch television after work, try getting up to stretch, lift weights, or jump rope during the commercials.

In addition to breaking up long periods of sitting, Dr. Basen-Engquist recommended 30 minutes of exercise each day. "For exercise, moderate intensity is better than light intensity," she said.

For people who cannot fit regular workouts into their schedules, she suggested taking three brisk 10-minute walks during the day. "Remember, it's important to get creative and find ways to stay active," Dr. Basen-Engquist said. ■

– J. Delsigne

FOR MORE INFORMATION

- *Ask your physician*
- *Visit www.mdanderson.org*
- *Read about the American Cancer Society study at http://pressroom.cancer.org/index.php?s=43&item=257*
- *For exercise tips, visit www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/prevention-and-screening/exercise/index.html*

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experienced progression-free survival for a median follow-up period of 34 months, compared with the 10%–15% that would be expected with surgery alone."

The study also revealed that the preoperative chemotherapy did not increase surgical complications and that the paclitaxel, ifosfamide, and cisplatin regimen was as effective as but less toxic than a combination previously used in a larger multicenter study by the cooperative trial group SWOG.

For patients who cannot tolerate or whose tumors do not respond to neoadjuvant chemotherapy, radiation therapy can be used to improve the resectability of nodal masses. Preoperative chemoradiation also can improve lymph node tumor resectability and is particularly useful in patients with fixed or bulky nodes.

"We also use radiation adjuvantly, usually with concurrent chemotherapy, when concerning features such as multiple involved nodes or gross extranodal extension are found at lymph node dissection," Dr. Hoffman said. "It is important to achieve local disease control in the pelvis to prevent morbid local recurrence."

Chemoradiation is also used as a definitive therapy in patients who refuse or are medically unable to tolerate surgery.

Toward better answers

An international collaborative research initiative of the U.S. National Cancer Institute, the United Kingdom clinical trial system, and the European Organization for Research and Treatment of Cancer is likely to clarify treatment options for penile SCC. This collaborative, called the International Rare Cancer Initiative, was formed in 2011 to provide a research infrastructure and recruit sufficient numbers of study participants from multiple international sites to help direct the treatment of rare cancers, including penile cancer. As part of this initiative, MD Anderson will participate in a collaborative study of metastatic penile cancer. ■

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