Transport Oncophysics Could Guide Pancreatic Cancer Treatment

By Jill Delsigne-Russell

Pancreatic ductal adenocarcinomas respond poorly to standard treatments. Researchers at The University of Texas MD Anderson Cancer Center are applying the principles of physics to characterize the tumors, and these analyses could lead to individualized therapy.

The relatively new discipline of transport oncophysics describes how the physical properties of individual tumors affect the transport of chemotherapy drugs to cancer cells.

Left: Computed tomography scans from two patients with pancreatic ductal adenocarcinoma show different contrast enhancement patterns in the normal pancreas and pancreatic tumor (circled). Right: Graphs derived from a mathematical model of transport properties illustrate changes over time in tissue density (measured in Hounsfield units [HU]) as a function of time (measured in seconds [s]) for each patient’s normal (blue line) and cancer (red line) tissues. Reprinted with the permission of the American Society for Clinical Investigation from J Clin Invest. 2014;124:1525–1536.
Pancreatic Cancer Treatment

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For example, gemcitabine must be able to cross vascular, extracellular, cellular, and molecular compartments to be effective. In some solid tumors, such as pancreatic ductal adenocarcinoma, certain physical characteristics in these transport mechanisms contribute to resistance to treatment.

“Onkos, the Greek root word for oncology, means mass,” said Eugene Koay, M.D., Ph.D., an assistant professor in the Division of Radiation Oncology. “The ancients knew that tumors have different physical properties than normal tissue, and recently, oncologists have been returning to the idea that these physical properties are a reflection of the underlying biology of tumors and may give us insight into patients’ prognosis and likelihood of response to specific treatments.”

Physical properties and barriers to treatment

About 80% of patients who have pancreatic ductal adenocarcinoma present with nonresectable disease, which is usually treated with chemotherapy drugs such as gemcitabine. But the response rates have been dismal, in part because physical barriers in the tumors prevent the effective delivery of gemcitabine and other cytotoxic chemotherapy drugs.

Unfortunately, biomarkers to predict response to specific treatments for pancreatic ductal adenocarcinoma are lacking. The only currently available biomarker is the serum CA19-9 level; an elevated level is associated with shorter survival. But testing for serum CA19-9 has several limitations, including poor sensitivity, false-negative results in patients who have the recessive allele for both types of Lewis antigens, and false-positive results in patients with obstructive jaundice.

Quantitative imaging assessment of transport properties

Transport oncophysics could help provide new biomarkers based on the physical characteristics of pancreatic ductal adenocarcinoma. Toward that end, Dr. Koay and his collaborators developed a mathematical model to measure mass transport properties using routine pancreatic-protocol, contrast-enhanced computed tomography (CT) scans of patients with pancreatic ductal adenocarcinoma. Researchers can use the mathematical model to track the changes in contrast enhancement between the phases of the CT scans.

Specifically, the model accounts for the variable density in tissue as a function of time; that is, changes in tissue density are measured by the transfer of contrast agent molecules through the vessel walls at certain rates and by rates of clearance from the vasculature. These calculations allow researchers to gain insight into the density of tumors’ stroma and vessels.

Dr. Koay and his colleagues used this quantitative technique in a clinical trial of intraoperative gemcitabine infusion in 12 patients with pancreatic ductal adenocarcinoma. Quantitative analysis of contrast-enhanced CT scans taken prior to surgery revealed a negative correlation between the degree of contrast enhancement in the tumors and gemcitabine delivery. The correlation is negative, Dr. Koay explained, because a high degree of enhancement indicates dense stroma, which impedes drug transport.

To further explore the relationship between CT findings and treatment outcomes, Dr. Koay and his colleagues retrospectively evaluated pretreatment contrast-enhanced CT scans of 110 patients who were treated with chemoradiation for pancreatic ductal adenocarcinoma in two clinical trials. The degree of enhancement on the CT scans was associated with pathological response to chemoradiation and overall survival, indicating that the transport properties of pancreatic tumors could be used as a biomarker. This information could be useful for therapeutic strategies aimed at the stroma and vasculature of pancreatic ductal adenocarcinomas.

Stromal density

Pancreatic ductal adenocarcinomas characteristically have dense stroma. Dr. Koay said, “The role of the dense stroma is complex. The stroma appears to partially impair pancreatic cancer cells from spreading to other organs, but it also serves as a barrier between chemotherapy and the tumor cells.” He also noted that the amount of stroma varies from patient to patient and from region to region within an individual tumor.

Variations in stromal density indicate a need to individualize therapeutic strategies that target the tumor stroma. Previous animal model studies of pancreatic cancer showed that depleting the stroma with agents that inhibit the hedgehog signaling pathway helped chemotherapy delivery, but patients treated with this stromal depletion strategy in a clinical trial had poorer survival outcomes than did patients treated with gemcitabine alone. However, this trial did not stratify patients by stromal density.

Quantitative imaging assessment of transport oncophysics could address the need for stratification in clinical trials and thus help to identify the pa-
patients most likely to benefit from certain treatment strategies. For example, in the intraoperative gemcitabine infusion trial, Dr. Koay’s group found that gemcitabine uptake had both a negative correlation with the density of the tumor stroma and a positive correlation with the uptake of human equilibrative nucleoside transporter 1 (hENT1), the primary transport protein that allows chemotherapy agents to enter the cellular compartment.

Pancreatic ductal adenocarcinoma is also characterized by an extensive desmoplastic response resulting in large stromal cells and abundant hyaluronic acid. Hyaluronic acid traps water, leading to high interstitial fluid pressure in the tumor stroma. This pressure becomes a barrier to effective chemotherapy delivery.

Investigators at other institutions are currently investigating whether enzymatic degradation of hyaluronic acid in pancreatic ductal adenocarcinoma can reduce interstitial pressure and improve chemotherapy delivery. Using quantitative imaging assessment to identify differences in stromal amount and composition could help identify patients who are most likely to benefit from this strategy. This is the subject of ongoing investigations in Dr. Koay’s laboratory.

**Vessel density**

Pancreatic ductal adenocarcinoma is also characterized by hypovascularity and resistance to radiation therapy. The resistance may result from multiple factors, including the relative hypoxia of the tumor, high interstitial fluid pressure, and intrinsic radioresistance of the tumor cells. Radiation itself induces the expression of vascular endothelial growth factor (VEGF), which contributes to hypoxia and thus may increase resistance to future radiation treatments.

Previous clinical trials at MD Anderson have attempted to use the VEGF inhibitor bevacizumab to sensitize pancreatic ductal adenocarcinoma to radiation therapy. Although most patients did not benefit from the addition of bevacizumab, several survived beyond 2 years. Patients in these trials were not stratified according to angiogenesis markers, but Dr. Koay hypothesizes that the patients who benefited from bevacizumab had denser microvascularity than the patients who did not benefit. Quantitative imaging assessment of vessel density could help identify the patients who might benefit from bevacizumab or other angiogenesis inhibitors, reinvigorating a “failed” treatment strategy for this disease for a subset of patients.

**Future directions**

Most of Dr. Koay’s previous studies of quantitative imaging assessment were retrospective, and he is currently validating quantitative imaging assessment prospectively as the principal investigator of a clinical trial at MD Anderson (PA14-0319 or NCT02361320). The trial is recruiting patients with unresectable or borderline resectable pancreatic cancer, and Dr. Koay hopes to have results within 2 years.

Dr. Koay is also working with large cooperative groups such as the Alliance for Clinical Trials in Oncology, SWOG, and NRG Oncology to integrate his methods into ongoing clinical trials. Quantitative imaging assessment of pancreatic tumors’ transport properties can provide insight before treatment begins, and this assessment does not add health care costs because CT scans are part of the routine work-up for this disease. Indeed, Dr. Koay’s work has been incorporated into the MD Anderson Moon Shot programs for pancreatic, colorectal, and lung cancers.

In addition to improving treatment planning, transport oncophysics may further the understanding of clinically relevant processes such as tumorigenesis and metastasis. “This is an exciting time for oncology and the concept of transport oncophysics,” Dr. Koay said. “Physicists and physicians are communicating and acknowledging that cancer is both biologically and physically different than healthy tissue, and the National Institutes of Health is supporting the use of the physical sciences to understand cancer. If we could combine quantitative imaging assessments with traditional biomarkers, we could rationally direct therapeutic strategies for patients and improve their outcomes.”

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FURTHER READING
Nivolumab Shows Potential in Treating Squamous Cell Carcinoma of the Anal Canal

By Brandon C. Strubberg

Currently, there are no standard therapy options for patients with treatment-refractory metastatic squamous cell carcinoma of the anal canal (SCCA), but early results of a multi-institutional clinical trial (No. NCI9673) led by researchers at The University of Texas MD Anderson Cancer Center show that the immunotherapy drug nivolumab may be effective against the disease.

“Although a rare malignancy, SCCA is on the rise and has a strong association with the human papillomavirus (HPV) and impaired immune function,” said Cathy Eng, M.D., a professor in the Department of Gastrointestinal Medical Oncology and the national trial’s principal investigator. She added that anal cancer rates increase 2%–3% each year.

About 20% of the more than 8,000 patients diagnosed with SCCA each year in the United States present with metastatic disease. Additionally, 20% of patients who have early-stage SCCA will later develop metastatic disease. Metastatic SCCA is typically treated with platinum-based chemotherapy; however, such regimens have not been fully evaluated in clinical trials for patients with metastatic SCCA, and there is no established standard of care for refractory metastatic disease.

Evaluating nivolumab

Nivolumab is a monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) by binding to the PD-1 ligand (PD-L1). PD-1 is an immune checkpoint that shuts down T lymphocyte attacks when activated by PD-L1. HPV-related anal cancer tumors have proteins produced by the virus, so nivolumab could help the immune system recognize and attack anal tumor cells infected with HPV.

The ongoing phase II clinical trial is the first study to evaluate the efficacy of nivolumab in the treatment of refractory metastatic SCCA. Dr. Eng said that the trial, which completed enrollment after only 5 months, addresses an unmet need for treatment.

Patients in the trial, all of whom have previously undergone at least one treatment for metastatic SCCA, receive nivolumab intravenously every 2 weeks until they experience disease progression or unacceptable toxic effects.

It was important to researchers that the patient population be representative of those whom SCCA typically affects, so HIV-positive patients were eligible provided that their CD4-positive T lymphocyte count was at least 300/µL. “Since HIV predisposes patients to compromised immune systems, it is a well-defined risk factor for anal cancer,” said Van Morris, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology.

Two HIV-positive patients were enrolled in the trial, making it the first completed trial of a PD-1 or PD-L1 inhibitor to include HIV-positive patients.

Top: Pretreatment computed tomography scans show metastatic tumors (arrows) from squamous cell carcinoma of the anal canal. Bottom: Scans of the same patient after 22 cycles of nivolumab show improvement. Images courtesy of Dr. Cathy Eng.
Early results
In an exploratory correlative study of tumor biopsy samples taken from nine patients before and during nivolumab treatment, pretreatment tumor samples from the five patients whose disease responded to nivolumab showed significantly higher percentages of CD3-positive and CD8-positive T lymphocytes compared with pretreatment samples from patients whose disease did not respond. Pretreatment tumor samples from the patients whose disease responded to nivolumab also had higher frequencies of CD8-positive T lymphocytes expressing PD-1 and CD45-positive immune cells expressing PD-L1 compared with pretreatment samples from patients whose disease did not respond. These exploratory findings, presented at the American Association for Cancer Research’s annual meeting in April, pointed to correlations between immunological biomarkers and responses to nivolumab treatment.

Clinical results for the trial were reported at the American Society of Clinical Oncology’s annual meeting in June. Of 37 patients evaluable for response, two had a complete response, seven had a partial response, and 17 had stable disease. These numbers add up to a 70% control rate and a 24% overall response rate. The median progression-free survival duration was 3.9 months.

No grade 4 toxic effects were observed among the patients treated with nivolumab; however, five occurrences of grade 3 fatigue, anemia, rash, and hypothyroidism were reported. Grade 1 or 2 fatigue, anemia, and rash also occurred. The HIV-positive patients did not experience any additional toxic effects.

Six patients currently remain in the trial, three at MD Anderson and three at other participating institutions. The trial is being amended to enroll additional patients later this year. “Our findings represent an exciting step forward for patients with no standard of care,” Dr. Eng said. “We now plan to extend our research further by looking at combined immunotherapy agents.”

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Laura Sussman contributed to this article.

Lymphedema Screening Initiative for Breast Cancer Survivors Offers Early Diagnosis, Treatment

By Jill Delsigne-Russell

Lymphedema can be a debilitating side effect of breast cancer treatment. To diagnose and treat the condition early, when it may be reversible, a program at The University of Texas MD Anderson Cancer Center identifies and screens patients at high risk for lymphedema.

Breast cancer surgery sometimes requires the removal of some or all of the axillary lymph nodes, and radiation therapy to the regional lymph nodes (which include the internal mammary, axillary, and supraclavicular lymph node beds) can damage the lymphatic system. When the body is unable to drain lymph, fluid can build up in the patient’s extremities; in breast cancer patients, this tends to occur in the arms.

“Lymphedema affects quality of life for our patients. Patients end up with arms that are much larger than normal and feel heavy and painful. Sometimes it’s difficult for these patients to fit into their clothes and to do their regular activities,” said Simona Shaitelman, M.D., an assistant professor in the Department of Radiation Oncology. “Unfortunately, if lymphedema is not diagnosed early, it’s nearly impossible to completely reverse the condition.”

Dr. Shaitelman encourages patients who are at high risk for lymphedema (i.e., those whose breast cancer treatment includes axillary lymph node dissection or radiation therapy to the regional lymph nodes) to see a physical therapist for an educational session right after treatment. She said, “Physical therapists can teach patients preventive exercises that they can do at home to reduce their risk of lymphedema, which really empowers patients.” Dr. Shaitelman also makes sure patients who are at high risk for lymphedema are included in long-term follow-up through the lymphedema screening initiative.

Lymphedema screening initiative

Dr. Shaitelman and her colleagues have established a lymphedema screening initiative at MD Anderson to diagnose this debilitating condition as early as possible. At the Breast Center, pretreatment arm measurements are taken via perometer for patients who will undergo any type of treatment to the lymph nodes. When high-risk patients return to MD Anderson for follow-up visits, arm measurements are included with the workup for other vital signs. If the arm measurement increases, the patient is referred to physical therapy.

Refining perometer use

To reduce measurement errors, two medical assistants are dedicated to lymphedema screening in the Breast Center and have been trained to use perometers, which employ infrared technology to measure arm volume and may enable detection of lymphedema earlier than standard tape measurements. However, after starting the initiative, Dr. Shaitelman and her colleagues found that the perometer measurements were not as reliable as had been expected.
Lymphedema Screening Initiative
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“We wanted to make sure that our results were reproducible so that we didn’t misdiagnose patients,” Dr. Shaitelman said. Toward this goal, she worked with Parviz Kheirkhah, Ph.D., a senior health care systems engineer in the Office of Performance Improvement, to optimize the perometer measurements. They added handlebars of different heights to the machine and to the wall near the machine; these handlebars help patients to remain stable and optimize their positioning for the measurements. The handlebars have decreased variability in perometer measurements by 28%.

Coordinating care
Patients at MD Anderson who have lymphedema are seen by physical therapists who are certified by the Lymphedema Association of North America. These patients typically undergo complete decongestive therapy, which includes manual lymph drainage and the use of compression garments. When complete decongestive therapy cannot control a patient’s lymphedema, the patient is referred to a plastic surgeon. Mark Schaverien, M.D., Edward Chang, M.D., and Matthew Hanasono, M.D., are among the faculty members in the Department of Plastic Surgery who specialize in microvascular techniques that can improve lymph drainage to relieve lymphedema.

“We’re working to improve our screening program so that we can begin to triage patients and systematically determine who should be referred to plastic surgery earlier,” Dr. Shaitelman said. “We’d like to take better advantage of the specialized skill set of our plastic surgeons and let patients know that this treatment option is available.” Ongoing research is expected to improve these screening and triage efforts.

Clinical trials
Sarah DeSnyder, M.D., an assistant professor in the Department of Breast Surgical Oncology, is the principal investigator at MD Anderson for a multicenter clinical trial (2014-0911) to determine whether bi impedance spectroscopy, which measures extracellular fluid, can detect subclinical lymphedema earlier than standard tape measurements, resulting in treatment at earlier stages and a lower rate of progression. The trial will also investigate factors associated with lymphedema progression (such as body mass index, seroma, smoking status, age, and air travel), evaluate time until progression requires complete decongestive therapy, and determine whether subclinical lymphedema detection and early intervention improve symptoms and quality of life compared with tape measurements and later intervention. The trial is enrolling patients who plan to undergo surgery for invasive breast cancer or ductal carcinoma in situ.

In another clinical trial, Drs. Shaitelman and DeSnyder along with Elizabeth Mittendorf, M.D., Ph.D., an associate professor in the Department of Breast Surgical Oncology, and Melissa Aldrich, Ph.D., an assistant professor in the Center for Molecular Imaging at The University of Texas Health Science Center at Houston, will investigate immune and inflammatory markers for lymphedema (2016-0170). The trial will soon begin enrolling patients with locally advanced breast cancer who will undergo axillary lymph node dissection and radiation to the regional lymph nodes. Using fluorescence imaging with microdose amounts of dye to visualize the lymph nodes in the patients’ arms, the trial aims to determine whether early changes in the lymphatic system are correlated with serum immune or inflammatory markers.

“We hypothesize that lymphedema is an autoimmune reaction,” Dr. Shaitelman said, adding that this hypothesis is supported by data from multiple fields. “Discovering immune-related biomarkers for lymphedema could help us further refine which patients are at high risk, counsel patients to reduce their risk of lymphedema, and find therapeutic targets.”

The findings from these trials, if validated, will be incorporated into the lymphedema screening initiative. Dr. Shaitelman said, “We want our initiative to be flexible and science based. With advances in technology for detecting and treating lymphedema, we hope to diagnose and treat patients early to reverse this condition.”

While current lymphedema screening and research programs focus on improving quality of life for breast cancer survivors, findings from these efforts could have applications for other cancer sites. As long-term data become available on the outcomes of breast cancer patients who participate in the lymphedema screening initiative, the program may be adapted to screen for lymphedema in patients with head and neck cancers, melanoma, or gynecological malignancies.

FOR MORE INFORMATION
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Health and Fitness Apps
Software tools can help you achieve wellness

If you own a smartphone, you almost certainly use apps, or applications. While many apps are geared toward leisure activities like online shopping or gaming, some apps can be used to improve your health. Cancer survivors may find these apps to be particularly useful.

Getting started
There are a few things to keep in mind when choosing an app. The first of these is cost. While many apps are free, some do cost money. Other apps are free to download but require payment in order to access premium features. Before you spend money on any app, it's a good idea to check the app's reviews to see how satisfied people were with the app.

Another important consideration when choosing an app is its data usage. Web content is often downloaded or uploaded by apps. If it is not connected to a Wi-Fi network, your smartphone will use cellular data to complete these tasks. While this is fine in small doses, using cellular data for apps can quickly add up and become expensive.

Also, apps and their data can take up a significant amount of storage space on your smartphone.

Types of apps
Exercise and nutrition apps
MapMyFitness is a popular workout tracking app that uses your smartphone's built-in GPS to monitor your route, speed, elevation, and calories burned when you run, walk, or cycle. Using this app is remarkably simple: after downloading it and setting up your account, all you need to do is open the app, turn tracking on, and carry your smartphone with you on your workout. More specialized apps in the same family include MapMyRun, MapMyWalk, and MapMyRide. MapMyFitness apps are free to download and use, but to access premium features, there is a charge of $5.99 per month or $29.99 per year.

Another popular exercise app is Fitbit. Unlike standalone apps, Fitbit can connect your smartphone and computer with your Fitbit device. The Fitbit device is a wearable fitness tracker that can track not only your workout but also your daily activity, food, and sleep. Fitbit devices start at $59.99, and optional premium features for the app cost $49.99 per year.

If you're trying to achieve specific health goals, you might want to try Lifesum. To get started, the app asks what your nutrition plan is—to be healthier, lose weight, or gain muscle. From there, you can begin inputting your diet and exercise information. The app will help you choose an exercise plan and give you feedback on how to pick foods and eat healthy portions to achieve your goals. Another feature of Lifesum is its hydration tracker, which gives you reminders to drink enough water to stay healthy. The Lifesum app is free to download, but access to the premium membership is $9.99 per month, $21.99 for 3 months, or $45.00 per year.

Another app that can help you improve your eating habits is Fooducate. To use Fooducate, you can download the free app and use your phone's camera to scan the barcodes of packaged food. The app assigns the food a letter grade—A, B, C, or D—based on the quality of its calories and may offer healthier alternatives. Fooducate is not affiliated with any diets, supplements, or manufacturers, but it does have in-app purchases.

Cancer-specific apps
While some health and fitness apps help you remain healthy, other apps are designed to help cancer patients during treatment. One such app, Cancer.Net Mobile, features oncologist-approved information from the American Society of Clinical Oncology. This resource for cancer patients and family members includes guides on 120 types of cancer, the latest news from Cancer.Net, and plenty of interactive tools. These allow you to jot down questions for doctors, record audio answers, save information about prescriptions, and track symptoms. The Cancer.Net app is free and allows you to create a passcode to protect your personal information. If you use an iPhone, you can also back up your information on the iCloud.

Some cancer centers offer mobile apps to help patients manage their care. For example, MD Anderson Mobile connects to the institution's electronic health record system, allowing patients or their caregivers to keep track of appointments, view personal health records, and communicate securely with their health care team from their smartphone or tablet.

While health and fitness apps aren't a cure-all, they can be useful tools to keep you motivated and on track to achieving your wellness goals.

—E. Nielsen

FOR MORE INFORMATION
- Ask your physician
- Call askMDAnderson at 877-632-6789
HPV-Associated Cancers Course

To help clinicians understand the scope of cancers related to the human papillomavirus (HPV), The University of Texas MD Anderson Cancer Center’s Professional Oncology Education program has developed a new HPV-Associated Cancers Course. The course can be taken online for continuing medical education (CME) credit at no cost.

The main goals of the course are to explain the biology of HPV and its association with various cancers and to provide recommendations and information about the prevention, screening, and treatment of HPV-related cancers.

The HPV-Associated Cancers Course comprises 10 lessons on the following topics:

- introduction to HPV-related diseases,
- biology of HPV,
- cervical cancer (3 lessons),
- anal cancer,
- oropharyngeal cancer (2 lessons),
- penile cancer, and
- HPV vaccination.

Each lesson includes a 20- to 60-minute lecture by an expert clinician or researcher followed by a brief quiz. The lessons provide an opportunity for clinicians with expertise in treating one HPV-related cancer to learn about other cancer types that they see less often. The importance of vaccination against HPV for both girls and boys is emphasized in the lessons, as the U.S. vaccination rate continues to lag behind those of other developed countries. Many clinicians will find the module about the biology of the virus to be particularly interesting, as it explains the difference between the low-risk and high-risk strains of the virus and the process of malignant transformation.

The entire HPV-Associated Cancers Course is available online at MD Anderson’s Professional Oncology Education Resources page at www.mdanderson.org/poe. Physicians and other health care professionals can sign in to take the course for CME credit, and anyone can view individual lectures without signing in.