Cleveland Clinic

Cancer Advances

Cleveland Clinic Cancer Center | Summer 2018

Better, Faster, Stronger:

Innovations in Breast Cancer Radiotherapy

Ranked No. 5 in America for cancer care by *U.S. News & World Report*.

Dear colleagues,

Treatment value rather than patient volume is now the driving force in American healthcare. At Cleveland Clinic Cancer Center, one of our priorities in this value-based shift is the alignment of care across our numerous locations. As you will read in my piece on page 24, we're using cancer programming to prioritize and structure different aspects of team-based care, including multidisciplinary clinics, tumor boards, care paths and reduction in time to treat, across our many locations. The work in this edition of *Cancer Advances* highlights the impact of our team-based care approach not just on patients, but on the future of cancer care.

Our cover story features the work of Chirag Shah, MD, whose precision approach to radiation oncology is setting new standards in breast cancer radiotherapy and improving the quality and value of care for patients (p. 3) in our Breast Cancer Program. A new imaging modality offers clinicians a noninvasive, accurate way to discriminate between some breast cancer tumor types (p. 18) and may potentially change the way we treat patients in this program.

Our multidisciplinary Liver Cancer Program team has pioneered transplant for liver metastases from colorectal cancer in the United States (p. 6). Our Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is testing several approaches to bypassing the blood-brain barrier and now offers a wide range of direct therapeutic delivery options to patients (p. 16).

Our Prostate Cancer Program continues its tradition of innovation in the development of a new biomarker by Nima Sharifi, MD (p. 23), and refinements in radiotherapy for high-risk postprostatectomy patients from Rahul Tendulkar, MD (p. 14). One of our new staff in the Genitourinary Cancer Program, Moshe Ornstein, MD, MA, offers an overview of the potential of immunotherapy frontline treatments for renal cell carcinoma (p. 12).

None of the work we do in our cancer programs would be possible without our physician scientists, including NCI Outstanding Investigator Jaroslaw Maciejewski, MD, PhD, and his work on genetic mutations in myelodysplastic syndromes (p. 22). Radiation oncologist and scientist Jennifer Yu, MD, PhD, is targeting the molecular mechanisms of brain cancer, from discovering key protein pathways to using these discoveries to develop algorithms that can distinguish tumor recurrence from radiation necrosis on MRI (p. 10). We also highlight the 24 promising projects awarded funds from VeloSano 4, which raised $4.17 million, 100 percent of which goes directly to our investigators for research (p. 26).

I welcome the opportunity to collaborate, to discuss new ideas and to answer your questions, from bench research to clinical trials to operations and strategies for optimal clinical alignment. If we can help you with a patient's care or a clinical issue, please let me know.

Sincerely,

Brian J. Bolwell, MD, FACP
Chairman, Taussig Cancer Institute
Cleveland Clinic Cancer Center
bolwelb@ccf.org | 216.444.6922
On Twitter: @BrianBolwellMD

Better, Faster, Stronger: Innovations in Breast Cancer Radiotherapy

One researcher's mission to make radiotherapy easier, more convenient, safer for women

(continued on page 4)

Table of Contents

Better, Faster, Stronger: Innovations in Breast Cancer Radiotherapy...3

Innovations in Liver Transplant for Liver and Colorectal Cancers...6

Chimeric Antigen Receptor T-Cell Therapy at Cleveland Clinic Cancer Center...9

Cancer Stem Cell Researcher Tackles Brain Cancers, from Protein Pathways to Imaging Algorithms...10

The Advent of Immunotherapy as Frontline Treatment for Renal Cell Carcinoma...12

Should Adjuvant Radiotherapy Be the Gold Standard for High-Risk Postprostatectomy Patients?...14

In Brain Tumor Therapeutics, Options for Bypassing the Blood-Brain Barrier Are Burgeoning...16

The Prognostic Potential of Optoacoustic Imaging in Patients with Breast Cancer...18

News Briefs...20

Mutations in Aplastic Anemia Can Predict Increased Risk of Myelodysplastic Syndromes...22

A New Biomarker for Guiding Prostate Cancer Treatment...23

Cancer Programming and Clinical Alignment...24

VeloSano Goes 100% for the Cure...26

New Staff...27

Resources for Physicians...28

Cover image: Accelerated partial breast irradiation

(CONTINUED)

Dr. Shah is Director of Clinical Research and Breast Radiation in the Department of Radiation Oncology.

He can be reached at shahc4@ccf.org or 216.445.8180.

On Twitter: @CShahMD

When Chirag Shah, MD, became a radiation oncologist in 2007, almost all breast cancer patients had one option: five to six weeks of daily, whole-breast/chest-wall radiation, regardless of surgical type (mastectomy or lumpectomy). A mere decade later, thanks to advances in the field refined in part at Cleveland Clinic Cancer Center, patients can choose among several options for radiotherapy, many of which are safer and shorter without compromising efficacy. Dr. Shah is directing Cleveland Clinic Cancer Center's adoption of new techniques to significantly reduce the duration of radiation therapy treatments for appropriately selected patients, from three to four weeks to just five treatments.

Intensity-modulated, accelerated partial breast radiation therapy

Accelerated partial breast irradiation (APBI) allows appropriately selected patients with early-stage breast cancer to complete adjuvant radiation in two weeks or less following breast-conserving surgery. To date, multiple randomized trials have demonstrated no difference in rates of recurrence or survival with APBI delivered using brachytherapy or external beam radiation techniques.

For patients with ductal carcinoma in situ (DCIS) and early-stage invasive breast cancer, APBI is an alternative to standard whole-breast irradiation, allowing for a reduction in the duration of radiation therapy. The technique, by reducing the amount of normal, healthy breast tissue treated with radiation, may also reduce side effects of treatment and improve cosmetic outcomes. It is also considered a cardiac and pulmonary dose-sparing technique.

One method of delivering APBI is intensity-modulated radiation therapy (IMRT), a highly precise form of radiotherapy. Cleveland Clinic Cancer Center employs a team of highly trained specialists that utilize the Edge® (Varian Medical Systems Inc.) radiosurgical system. The Edge is a linear accelerator coupled with real-time motion management to ensure fast, precise delivery of treatment. The six-degrees-of-freedom couch, which allows motion in multiple directions, permits accurate patient positioning, while a CT scanner attached to the machine allows accurate targeting of the area at risk.

"Combining active breathing control (ABC) with IMRT increases accuracy and reduces cardiac dosing even further," says Dr. Shah, Director of Clinical Research and Breast Radiation in the Department of Radiation Oncology. "We can usually line this up with an accuracy of within a few millimeters."

IMRT is commonly used to treat prostate, head and neck, and central nervous system cancers. Dr. Shah's team is refining its use in breast cancer to deliver partial breast irradiation. IMRT can deliver higher doses with fewer side effects and reduced treatment toxicity, but it does require more planning than traditional methods. "Even so, we've submitted a study showing that our five-fraction treatment reduces costs for patients and health systems. Although it uses more advanced technology, it saves money because of fewer treatments, less time in treatment, less missed work and reduced overall expenses," says Dr. Shah.

How to select appropriate patients

Dr. Shah led a group of physicians appointed by the American Brachytherapy Society to develop a consensus statement of updated guidelines for the appropriate and safe use of APBI, published in *Brachytherapy*. The new guidelines recommend the technique for a broader group of patients by expanding eligibility to younger patients as well as all patients with DCIS who meet the other criteria. The authors agree that the appropriate candidates for APBI meet the following criteria:

- Patients aged 45 years or older
- All invasive histologies and DCIS
- Tumors 3 cm or less
- Node negative
- Estrogen receptor positive or negative
- No lymphovascular space invasion
- Negative margins

"These guidelines allow for the selection of patients who can finish radiation therapy in two weeks or less, compared with the traditional period of three to six weeks, and potentially giving them a reduction in side effects, depending on the APBI technique," says Dr. Shah.

The previous APBI guidelines were developed in 2013, also led by Dr. Shah. Since then, results from newly published randomized trials, including RAPID, IMPORT LOW, University of Florence, ELIOT and TARGIT-A, have necessitated an update to the guidelines.

Cardiac dosing 50 percent below national average

Dr. Shah's research also focuses on other cardiac-sparing radiotherapy techniques for breast cancer. Cardiac toxicity after radiotherapy can include a range of conditions, from valvular disease to coronary artery disease and arrhythmias. While techniques targeting a smaller area like APBI (which Cleveland Clinic performs using IMRT) and intraoperative radiotherapy are important for reducing cardiac exposure to radiation, Cleveland Clinic Cancer Center also employs a variety of additional techniques to further minimize cardiac toxicity after radiotherapy for patients requiring more comprehensive radiation therapy to the whole breast/chest wall.

Deep inspiratory breath hold (DIBH)

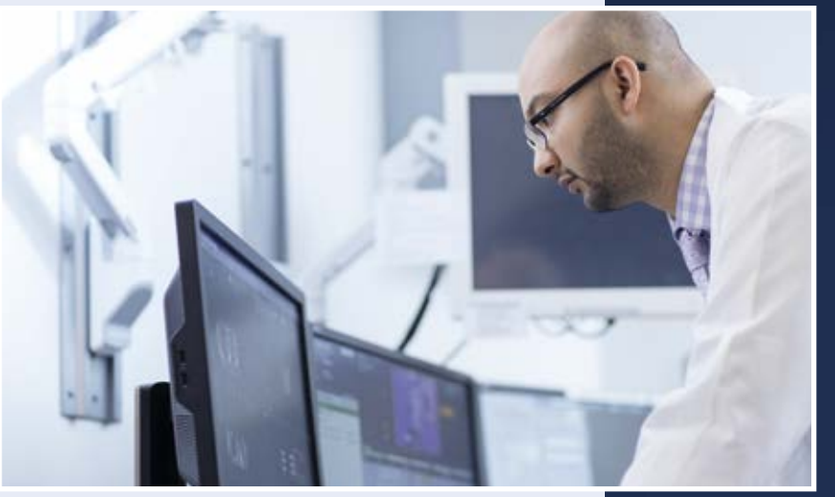
"The timing of radiotherapy with respect to the breathing cycle can make a clinically significant difference in the dose the heart receives," says Dr. Shah. "We incorporate this timing into our treatment planning by having patients perform a deep inspiratory breath hold during the CT scan used for planning, and we can estimate doses to the heart and observe the benefit with DIBH as compared to without." For daily treatment, the ABC system tracks the patient's breathing, using inspiratory volume as a surrogate for the distance between the heart and the breast. At the designated distance, the radiation is delivered. Surface-guided radiation therapy is used to ensure that the technique is delivered with accuracy.

Prone technique

Prone patient positioning allows the breast to fall away from the chest wall, increasing the distance of the radiation beam from the heart and reducing cardiac dose. "It's especially useful for patients with large breasts," says Dr. Shah. "It doesn't make as big of an impact as using breathing techniques such as DIBH, but it can be beneficial for a subset of patients."

Heart blocks

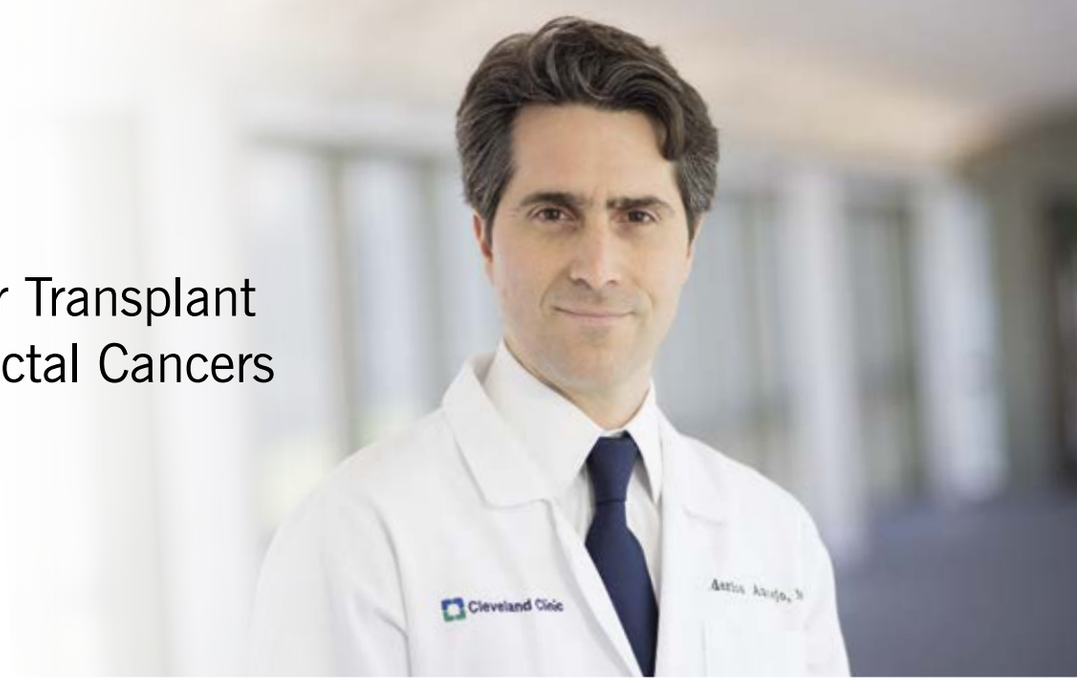
Heart blocks are another strategy to reduce cardiac dose. During treatment planning, Dr. Shah and the team block the heart using computer-programmed leaves inside the linear accelerator. The advances in programming allow blockage of the left ventricle without sacrificing dosing to the breast/chest wall. Using blocks allows for further reduction in heart dose, and they can be used with DIBH and other techniques.



The team is preparing data for publication showing that cardiac doses at Cleveland Clinic are lower than the national standard by more than 50 percent. "If you exclude the most complicated cases treating targets near the heart, the average is closer to a 75 percent reduction," says Dr. Shah. "We're really proud of what we've been able to achieve for our patients using a combination of cardiac-sparing techniques."

The next step, says Dr. Shah, is working with colleagues in medical oncology and cardiac oncology to study the impact of breast cancer treatment on the heart in a multidisciplinary manner. "We're looking at the impact of treatment factors such as radiation and chemotherapy, as well as nontreatment factors such as high blood pressure, high cholesterol — really a variety of factors to identify a way to risk-stratify breast cancer patients and survivors and determine the optimal treatment and cardiac follow-up regimens for each patient," says Dr. Shah.

With a variety of innovations and radiation technique trials available to patients, Dr. Shah is optimistic about the ability of breast radiation oncology to increase its impact on patient survival and quality of life. "In the short years I've been practicing, the field has exploded with better options for patients, and I believe we've only just begun."



Innovations in Liver Transplant for Liver and Colorectal Cancers

Patients with cancer in the liver — either from hepatocellular carcinoma (HCC) or colorectal cancer (CRC) metastases — face poor prognoses. An innovative liver transplant program at Cleveland Clinic Cancer Center is trying to change that by developing new models for assessing HCC patients for transplantation and performing the first transplant to treat liver metastases from CRC in the U.S.

Dr. Aucejo is Surgical Director of Cleveland Clinic's Liver Cancer Program.

He can be reached at aucejof@ccf.org or 216.444.6664.

On Twitter: @FAucejo

First in the U.S.: Transplant for liver metastases

More than 50 percent of patients with CRC will develop liver metastases. While the standard treatment for this condition is liver resection, only a third of patients are candidates for surgery. Surgery provides a five-year survival rate of 25 to 60 percent for this small subset of eligible patients. The remaining majority are treated with systemic chemotherapy. However, the five-year survival rate for systemic chemotherapy is only about 10 percent, with a median survival of about 24 months.

To improve patient outcomes, physician-researchers at Cleveland Clinic developed a new transplant protocol for treating liver metastases from colorectal cancer. Under the leadership of Federico Aucejo, MD, Surgical Director of Cleveland Clinic's Liver Cancer Program, Cleveland Clinic surgeons implemented the protocol to treat a patient with unresectable liver metastases from CRC, marking the first time that liver transplant surgery was performed for this indication in the U.S.

"Incorporating liver transplantation as a treatment option would allow the surgical management of liver metastases that cannot be treated with liver resection," explains Dr. Aucejo. "In line with initial worldwide experience, if we can demonstrate optimal mid- and long-term post-transplant survival, we will be positioned to prolong substantially the life span of a significant number of patients."

The new protocol

Cleveland Clinic began developing its new surgical protocol based on a 2013 University of Oslo published pilot study including 21 patients. The results of the study showed that liver transplantation helped CRC patients with unresectable liver metastases achieve a five-year survival rate of 60 percent.

Once the new protocol was developed, Cleveland Clinic found a perfect candidate for the first surgical application. This patient had unresectable metastases in the liver as well as liver disease from long-term chemotoxicity. The patient's cousin served as the live liver donor. Following the successful procedure, both patient and donor were discharged from the hospital within the expected time frame.

Incorporating an implantable chemotherapy infusion pump

Along with the new transplant protocol, the Liver Cancer Program incorporated a hepatic artery chemotherapy infusion pump protocol for patients with disease limited to the liver. So far, doctors have performed 20 pump implantations in combination with liver surgery to treat metastases from CRC. In addition to systemic chemotherapy, patients receive a chemotherapy pump that is implanted into the abdominal wall. The pump is connected to a catheter inserted into one of the arteries that connects to the liver.

By infusing chemotherapy directly into the liver, the infusion pump treats liver metastases more efficiently

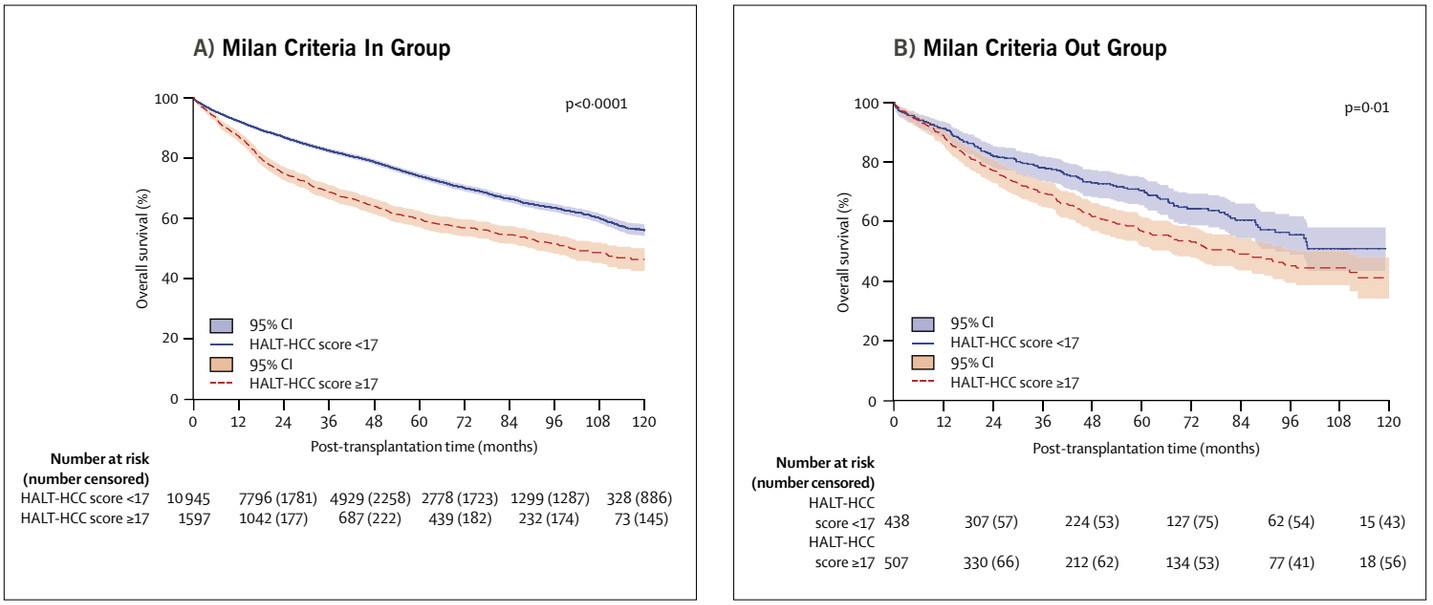


Figure. Kaplan-Meier curves for HALT-HCC scores less than 17 vs. 17 or more (A) if within Milan criteria and (B) if outside Milan criteria.

Figure and caption republished with permission from *The Lancet Gastroenterology & Hepatology*.

by preventing tumor recurrence after surgery or by reducing the bulk of disease so that it can be removed using surgery.

"Moving forward, we expect that liver transplant and hepatic artery chemotherapy pump protocols will complement each other," explains Dr. Aucejo. "Directed chemotherapy to the liver via an implantable pump will help limit disease to the liver over time. When chronic liver disease from long-term chemotoxicity develops, salvage liver transplantation will be the next step to consider."

Proving long-term efficacy and shifting to cadaver donors

Now that the new protocol has been successfully used on two patients, the next phases involve proving its long-term efficacy and shifting to cadaver donors. "Initially, we are using live donors for transplants due to the uncertainty of the long-term oncological outcome. This uncertainty stems from the close association between immunosuppression therapy and post-transplant tumor recurrence," explains Dr. Aucejo. "If our initial experience performing liver transplantation in patients with liver metastases from colorectal cancer using live donors is promising, accessing the cadaveric pool will become easier in the future.

"From an oncological standpoint, our goal is to achieve a five-year survival rate of at least 50 percent," reveals Dr. Aucejo. "If we can prove that the new protocol results in that kind of survival rate, we will be able to formally expand the indication for liver transplantation."

Transforming patient outcomes and prolonging survival

"The whole concept of using advanced surgical protocols to treat liver metastases from colorectal cancer is a way to transform the condition from a fast-moving and fatal disease to a chronic condition with prolonged patient survival," says Dr. Aucejo. "As a result, we speculate that by extending patient survival through aggressive surgical and locoregional therapies, novel and more effective systemic therapies will develop and increase survival even further."

Moreover, with emerging personalized medicine platforms utilizing clinical and molecular biomarkers that Cleveland Clinic Cancer Center is developing, improved patient selection criteria would be applied to achieve superior outcomes.

The first continuous risk score for liver cancer

HCC is the fifth leading cancer diagnosis worldwide and the fastest rising cause of cancer-related deaths in the U.S. For patients who are not candidates for hepatectomy (liver tumor resection), the only potentially curative option is liver transplantation. Given the limited number of donated organs, choosing the most appropriate candidates is critical.

(continued on page 8)

(CONTINUED)

"When liver cancer recurs after liver transplantation, the outcome is dismal, and because organs are limited, we need to allocate them to patients who can benefit most," says Dr. Aucejo.

The need for different assessment criteria

For two decades, the Milan criteria have been the gold standard for selecting liver cancer patients as transplant candidates. However, the Milan criteria have significant drawbacks: They only assess tumor morphology, such as size and number of tumors, and do not consider tumor biology, the patient's overall health or changes in oncological risk over time.

With a goal of overcoming the limitations of the Milan criteria, Dr. Aucejo and colleagues developed a new scoring system for assessment of overall survival following liver transplantation for liver cancer: HALT-HCC (Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma).

A look at HALT-HCC

HALT-HCC includes the following criteria:

- MELD-sodium (MELD-Na)
- Tumor burden score (TBS) — a tumor morphological score consisting of maximum tumor diameter and tumor number
- Alpha-fetoprotein (AFP)

To assess HALT-HCC, the research team conducted a retrospective cohort analysis using data from 420 patients with liver cancer who underwent liver transplantation at Cleveland Clinic between January 2002 and November 2014. Using multivariate Cox regression analysis, a risk equation was generated based on the association of HALT-HCC variables with overall survival. In the cohort, prognosis worsened with increasing HALT-HCC score.

Further risk assessment and validation were performed using nationwide data for the same time period from the Scientific Registry of Transplant Recipients based on a cohort of 13,717 patients. Patients within and outside the Milan criteria showed a similar risk of death when stratified by the HALT-HCC score.

How the new assessment tool performs

Overall, the HALT-HCC model outperformed traditional selection criteria on both data sets on a variety of statistical metrics. The study findings appear in *The Lancet Gastroenterology & Hepatology*.

"The findings show that HALT-HCC criteria provided more risk stratification compared with other existing criteria. It can predict more accurately the risk of dying after transplantation. In that way, it is clearly superior," says Dr. Aucejo.

This study established, for the first time in the field, the concept of a continuous multivariable risk measure for liver transplantation in patients with HCC. A major advantage of this model is that it can incorporate changes in the patient's oncological risk over time and therefore predict who has the best chance of living longer after transplantation. HALT-HCC could also be a metric to assess response to locoregional therapy. For example, a patient whose tumor has a good response to locoregional treatment could move higher on the waitlist for organ transplantation.

Since the first two studies were completed, the research team has continued its assessment and validation of HALT-HCC. It has recently completed a multicenter study in the U.S. and another international study including 4,000 patients from centers in the U.S., Canada, Europe and Asia. One of these studies, demonstrating the advantage of the HALT-HCC model in response to locoregional therapy to predict post-transplant outcomes, has been recently published in *Hepatology*.

Next steps

The final steps to acceptance of this new selection criteria are advanced statistical simulation modeling adapting to diverse regional patient waitlist times and evaluation through large prospective studies.

"Based on the results so far, HALT-HCC is practical and easy to implement and outperformed other selection criteria. It has the potential to become a new clinical tool that can lead to more efficient use of donated organs," says Dr. Aucejo.

Cleveland Clinic Liver Cancer Center of Excellence Research Program

Under the Liver Cancer Translational Research Program, with the prospective collection of centralized clinical data and investigation of biomarkers from biological specimens (tumor tissues, blood/serum samples, and breath exudate and saliva samples), a main goal is to develop precision medicine platforms to provide more effective care paths oriented to patients with liver cancer. Our researchers are working on refining liquid biopsy technology to improve diagnostics and response to treatments. Altogether, these advances are expected to elicit a substantial impact on the outcome of liver cancer patients in the near future, Dr. Aucejo says.

Chimeric Antigen Receptor T-Cell Therapy at Cleveland Clinic Cancer Center

Cleveland Clinic Cancer Center is now accepting patients for the FDA-approved chimeric antigen receptor (CAR) T-cell therapy, Yescarta™ (axicabtagene ciloleucel).

Yescarta is a CD19-directed CAR T-cell therapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy (including autologous stem cell transplantation). This includes diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Cleveland Clinic participated in the pivotal phase 2 trial that reported outcomes on 111 patients with relapsed or refractory large B-cell lymphomas.[1] Yescarta was administered to 101 patients (91 percent) with an objective response rate of 82 percent and a complete response rate of 54 percent. At 18 months post-treatment, the overall survival rate was 52 percent.

Severe side effects have been noted, prompting the FDA to require any centers that dispense Yescarta to be specially certified. These serious potential side effects include cytokine release syndrome and neurologic toxicities, both of which can be life-threatening. Building on experience obtained from participation in Yescarta clinical trials, Cleveland Clinic has established a multidisciplinary expert team with training and familiarity in administering this therapy and managing its toxicities.

Patients with relapsed or refractory large B-cell lymphoma should be referred for a consultation, preferably prior to initiating second-line therapy. Earlier referral allows us to expedite eligibility evaluation for Yescarta in case the patient does not respond to salvage therapy. Patients with more advanced disease should be referred as soon as possible, including patients whose lymphoma has relapsed or not responded after autologous or allogeneic stem cell transplantation.

For questions about our approach to this therapy, please contact Brian Hill, MD, PhD, or Navneet Majhail, MD, MS.

Dr. Majhail is Director of the Blood and Marrow Transplant Program.

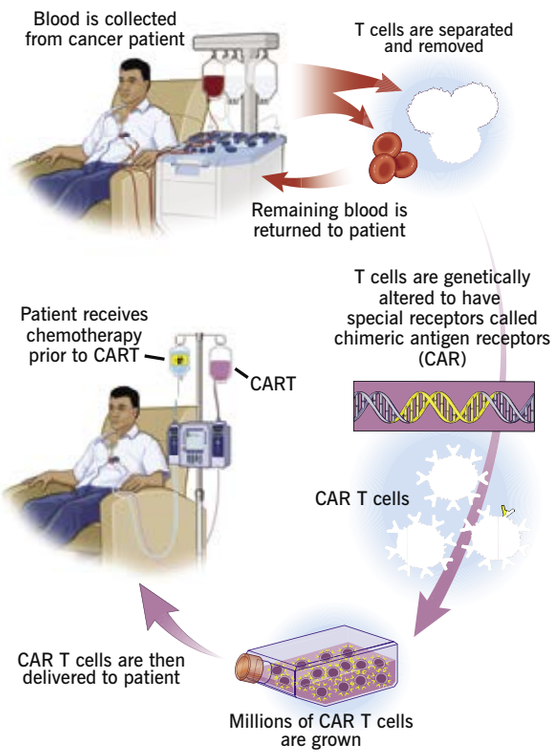
He can be reached at majhain@ccf.org or 216.444.2199.

On Twitter: @bldcancerdoc

Dr. Hill is Director of the Lymphoma Program.

He can be reached at hillb2@ccf.org or 216.445.9451.

On Twitter: @BrianHill_MDPhD



Reference

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

Cancer Stem Cell Researcher Tackles **Brain Cancers**, from Protein Pathways to Imaging Algorithms

Dr. Yu is staff in the Department of Stem Cell Biology and Regenerative Medicine in the Lerner Research Institute and the Department of Radiation Oncology, Cleveland Clinic Cancer Center.

She can be reached at yuj2@ccf.org or 216.445.9799.

A multifaceted approach to glioma tumors

Much of the research of Jennifer Yu, MD, PhD, explores the molecular mechanisms of brain cancer. Navigating the complex interactions among molecules in a cell that can trigger particular processes — perhaps turning a gene on or off or nurturing particular cell types — isn't always easy to describe succinctly, so she likes to use analogies whenever possible.

For instance, when Dr. Yu, Department of Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, and Department of Radiation Oncology, Cleveland Clinic Cancer Center, describes her work on cancer stem cells (CSCs), she evokes the image of a queen termite. Unless the queen is eliminated, the colony will survive; the same is true of cancer stem cells. Unless treatment targets those, there may be recurrences.

CSCs are elusive and difficult to destroy, especially CSCs that reside in hypoxic areas of tumors where radiation and chemotherapy are less effective. With this in mind, Dr. Yu and colleagues recently undertook an investigation to learn more about the molecular mechanisms of CSCs in hypoxic regions of glioma tumors.

The team first studied human glioma samples from a tissue database to identify candidate proteins that might be involved in this pathway. They found that a protein called vasorin — known to be induced in hypoxic settings — was abundant in patients with aggressive brain cancers who had poorer survival.

Next they studied vasorin in cell culture to determine how it affects glioblastoma (GBM) progression. Under normal conditions, an adaptor protein binds to and inhibits the pro-cancer Notch pathway (important for cell proliferation, differentiation and survival). They found that in a hypoxic environment, however, the abnormally abundant vasorin instead binds to and switches on the Notch signaling pathway in glioblastoma stem cells, leading to unchecked tumor growth (Figure 1). "I think with vasorin we found an Achilles heel for the glioma stem cells in these hypoxic areas," Dr. Yu says.

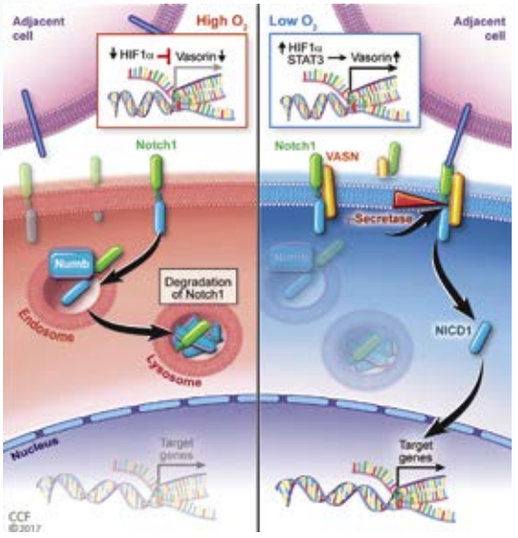


Figure 1. Hypoxia preferentially augments Notch signaling in glioma stem-like cells by inducing the *HIF1*/*STAT3* target protein vasorin. Vasorin functions as a competitive inhibitor of Numb to reduce Notch turnover, augmenting Notch signaling under hypoxic stress.

The research, which was supported by a $1.7 million NIH grant and published in *Cell Stem Cell*, is one of many projects that Dr. Yu has undertaken in her quest to better understand brain cancer and methods for treating it. In addition to molecular investigations, she also has projects looking at radiomics and radiation necrosis (RN) in brain cancer patients and the use of hyperthermia to treat brain tumors.

"About one-third of cancer patients will develop brain metastases," Dr. Yu says. "The aim of my lab is to understand how these metastases adapt to their environment at the molecular level and how we can target them effectively."

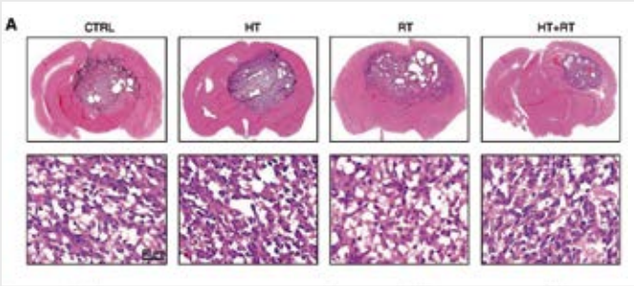


Figure 2. Thermoradiotherapy suppressed GBM growth and increased survival.

Representative images of cross-sections (hematoxylin and eosin stained) of mouse brains harvested on day five after treatment.

Originally published in *Cancer Research,* 75(8).

Algorithm to find brain tumors on MRIs

As part of that work, Dr. Yu teamed up in 2017 with Pallavi Tiwari, PhD, assistant professor of biomedical engineering at Case Western Reserve University, on a machine-learning project that will make it easier for neuroradiologists to differentiate changes on an MRI that could indicate RN or tumor recurrence.

"After radiation, a small percentage of brain tumor patients develop radiation necrosis that presents as radiographic changes on their MRIs," she says, "and it's very challenging to distinguish whether those changes are tumor progression or radiation necrosis."

Because both the symptoms and the MRI changes are similar among patients with RN and patients with tumor progression, physicians face a difficult scenario. "Should we go ahead and re-treat the patient for a recurrent tumor?" Dr. Yu says. "Or do we give steroids to treat the radiation necrosis?"

Dr. Tiwari's team created a new computational imaging technique called CoLlAGe that can better distinguish between the two conditions when they are illustrated on an MRI. Dr. Yu is now helping them refine that technique, an algorithm designed to detect the subtle signs of greater chaos that tumors, but not RN, display on MRIs. She and Dr. Tiwari are in the first year of that three-year project, which is funded by the Dana Foundation.

Preliminary studies have shown the algorithm can improve neuroradiologists' accuracy in interpreting the MRIs from 50 percent to 80 percent, Dr. Yu says. "We'd like to make it even more accurate."

Thermal medicine and glioblastoma

In addition, Dr. Yu has also recently conducted animal studies and clinical trials on hyperthermia and brain tumors. She currently serves as the vice president of the Society for Thermal Medicine.

"Heat has been used since ancient times to fight off all kinds of diseases: cancers, infections and other types of illness. We still use it, and now the technology is so much better," Dr. Yu says. "For instance, there are different ablative treatments for cancer — ultrasound ablation, laser ablation, radiofrequency ablation. With those ablative treatments, the heat itself is high enough to cook the cancer cells."

With other hyperthermic treatments, Dr. Yu says, lower temperatures are used. In those cases, the heat does not kill off the cancer cells outright but can prime them to make them more susceptible to radiation and chemotherapy.

In a 2015 study in *Cancer Research,* Dr. Yu and her colleagues studied how hyperthermia affected glioma stem-like cells (GSCs), a subpopulation of cells in tumors that are believed to mediate self-renewal and relapse in GBM.

The team showed that after radiation therapy, GSCs use the PI3K–AKT cell signaling pathway to extend their survival, but when they are exposed to hyperthermia beforehand, oncologists can suppress that pathway (Figure 2). This suppression makes the GSCs more sensitized to the radiation, allowing more cells to be killed. "When we did this in animal models," Dr. Yu says, "we were able to extend animal survival just by giving the combination of heat and radiation."

That work inspired the team to open a phase 0 clinical trial aiming to shorten the sequence between laser thermal therapy and adjuvant treatment for patients with GBM. Shortening that period would allow oncologists to take advantage of the biological properties of the heat therapy — sensitizing the GSCs to radiation, augmenting the immune system to fight the cancer and allowing the breakdown of the blood-brain barrier so chemotherapy can reach the tumor bed in the brain more effectively.

(CONTINUED)

"Hyperthermia is a very powerful technique," Dr. Yu says. "We need more people educated and trained in thermal therapy. There are very few centers across the U.S. that offer this type of treatment."

Finding targets to destroy cancer stem cells

Though Dr. Yu's research interests regarding brain cancer are broad, her main research area is enhancing understanding of GBM and GSCs. GBM is the most common primary brain tumor and is fatal despite multimodal therapy. GSCs — which have a high capacity for self-renewal, survival under hypoxic conditions and resistance to radiation, and high invasive potential — are a big reason the disease is so deadly.

Dr. Yu has studied how GSCs co-opt core development pathways like the Notch pathway, how they adapt to hypoxic environments, how they resist radiation and how noncoding RNAs contribute to GSC maintenance.

Her long-term goal is to find therapeutic sites, and her recent vasorin work has the potential. Her team has undertaken preclinical tests that showed blocking vasorin in mice led to reduced Notch signaling and longer survival, suggesting that vasorin is a viable target for the development of new treatment options to combat brain cancer.

"Killing glioblastoma stem cells is key to curing brain tumors," Dr. Yu said. "More studies are needed, but perhaps inhibiting vasorin can be used in conjunction with radiation therapy or chemotherapy in the future."

Now to find that inhibitor. Says Dr. Yu, "We are just getting started."

The Advent of **Immunotherapy as Frontline Treatment** for Renal Cell Carcinoma

A shifting paradigm

By Moshe C. Ornstein, MD, MA

Dr. Ornstein is associate staff in the Genitourinary Cancer Program at Cleveland Clinic Cancer Center.

He can be reached at ornstem@ccf.org or 216.445.6592.

On Twitter: @MosheOrnsteinMD

For more than a decade, the standard of care for the treatment of metastatic renal cell carcinoma (mRCC) had been fairly well-established. Although a small subset of patients were treated with high-dose interleukin-2 (IL-2), the majority of patients were treated with targeted therapies such as pazopanib (anti-VEGF), sunitinib (anti-VEGF) and temsirolimus (mTOR inhibitor). These agents target specific pathways implicated in RCC progression.

The first immunotherapy approval in mRCC since IL-2 was nivolumab (anti-PD-1 antibody), which the FDA approved in November 2015 for the treatment of patients with mRCC who had received prior anti-angiogenic therapy. However, despite the approval of nivolumab in previously treated mRCC patients, the use of checkpoint inhibitor immunotherapy has not yet been established in treatment-naïve mRCC.

The potential of immunotherapy in the frontline setting

Given the success of nivolumab in previously treated mRCC patients as well as the known immunosensitivity of mRCC to IL-2 in the frontline setting, multiple immunotherapy trials for treatment-naïve mRCC are in process. These trials include the combination of checkpoint inhibitors with targeted therapies as well as the combination of multiple checkpoint inhibitors with varying mechanisms of action. Two such trials were conducted in part at Cleveland Clinic Cancer Center.

Combining two checkpoint inhibitors: Checkmate 214

Checkmate 214 was an international, randomized phase 3 trial in which 1,096 treatment-naïve mRCC patients were randomized in a 1:1 fashion to receive the standard of care — frontline anti-VEGF therapy

sunitinib — versus the combination of two checkpoint inhibitors, ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1). The trial's primary endpoints of overall response rate (ORR), progression-free survival and overall survival (OS) were focused on the intermediate- and poor-risk patients.

Impressively, with a median follow-up of 25.2 months, the median OS (mOS) for intermediate- and poor-risk mRCC patients receiving combination ipilimumab/nivolumab was not reached, compared with an mOS of 26 months for those treated with sunitinib. Similarly, the ORR and complete response (CR) rates in the ipilimumab/nivolumab versus sunitinib groups were 42 versus 27 percent and 9 versus 1 percent, respectively.

These impressive response rates, combined with the CR rate and unreached mOS, position combination ipilimumab/nivolumab as a potential new standard of care for intermediate- and poor-risk patients with mRCC. These results were recently published in the *New England Journal of Medicine,* and the FDA approved ipilimumab/nivolumab for frontline treatment of intermediate- and poor-risk mRCC in April 2018.

Combining checkpoint inhibitors with targeted therapy: JAVELIN 100

JAVELIN 100 was an international phase 1b dose-finding and dose-expansion trial investigating the combination of avelumab (anti-PD-L1) and axitinib (anti-VEGF). *The Lancet Oncology* recently published preliminary results from the trial with Brian Rini, MD, Director of Cleveland Clinic Cancer Center's Genitourinary Cancer Program, as senior author. No unexpected safety signals emerged, and the therapy was well-tolerated overall. All six patients in the dose-finding phase had an objective response to therapy. Of the 49 patients in the dose-expansion cohort, 26 (53 percent) had an objective response.

The safety profile and preliminary antitumor activity in this phase 1b trial are extremely promising and suggest that combination targeted therapy/immunotherapy is safe and effective in treatment-naïve mRCC patients. The phase 3 JAVELIN 101 trial investigating the comparative effectiveness of the combination of avelumab and axitinib versus sunitinib for mRCC frontline therapy is ongoing.

Unanswered questions

As immunotherapy invades the frontline setting for mRCC, a few important clinical questions remain. Do all patients require combination therapy similar to the regimens in Checkmate 214 and JAVELIN 100, or can we identify patients who will respond just as well to monotherapy? Similarly, with combination regimens poised to be standard therapy in the frontline setting, defining the new standards for subsequent therapeutic options is critical. Another pressing question relates to the duration of therapy required for patients who respond to immunotherapy. It is well-known that some patients will have sustained responses to only a few doses of therapy, so it's important to identify which patients can discontinue therapy or take extended treatment breaks. These questions and a host of others are being investigated in clinical trials at Cleveland Clinic and at cancer centers around the world.

New hope for patients with mRCC

Although many patients respond to the current standard of care of targeted therapies as initial therapy for mRCC, the majority of patients will ultimately develop resistance. The benefit of immunotherapy in frontline mRCC therapy is potential improvement in response rates, complete responses and durability of response to therapy. As multiple frontline trials of checkpoint immunotherapy in combination with either targeted therapies or other checkpoint inhibitors are beginning to demonstrate promising results, there is newfound hope for patients with mRCC.

Should **Adjuvant Radiotherapy** Be the Gold Standard for High-Risk Postprostatectomy Patients?

New evidence supports ART, but caveats remain

Dr. Tendulkar is staff in the Department of Radiation Oncology. He can be reached at tendulr@ccf.org or 216.445.9869.

On Twitter: @RTendulkarMD

In a study published in *JAMA Oncology*, radiation oncologist Rahul Tendulkar, MD, and coauthors found that adjuvant radiotherapy (ART) for high-risk postprostatectomy patients is associated with superior outcomes compared with early-salvage radiotherapy (ESRT) along three key parameters: freedom from biochemical failure, distant metastases and overall survival.[1] While the potential side effects of radiation (sexual, urinary and bowel dysfunction, primarily) still present an argument for the wait-and-see approach, this study provides greater clarity for oncologists as they consider odds and options for their patients.

Approximately two-thirds of men who undergo a prostatectomy are cured of cancer, but the other third will present with recurrent disease within 10 years. The risk of recurrence rises to between 40 and 70 percent with adverse pathology, such as positive surgical margins, seminal vesicle invasion and extraprostatic extension. Treatment plans have traditionally leaned toward a wait-and-see approach with these high-risk patients — monitoring PSA levels and intervening with salvage radiotherapy when the kinetics of PSA levels or other changes signal a probable recurrence. The ART approach, on the other hand, is pre-emptive, before any of these signals manifest.

Setting the stage for more robust evidence

Dr. Tendulkar and his team retrospectively analyzed a large cohort of patients over multiple sites, with a longer follow-up duration, to see if a clearer picture emerged. To this end, they studied 1,566 patients seen across 10 leading medical centers between 1987 and 2013, with median follow-up of 65.8 months for the ART cohort and 73.3 months for the ESRT cohort.

These key findings emerged:

- Freedom from biochemical failure was 69 percent with ART versus 43 percent with ESRT.
- Freedom from distant metastases was 95 percent with ART versus 85 percent with ESRT.
- Overall survival rate was 91 percent with ART versus 79 percent with ESRT.

The cohort size, time span and high caliber of the participating medical centers strengthen the study's findings. But Dr. Tendulkar explains that it is still an apples-to-oranges comparison, with one procedure being pre-emptive and the other triggered by symptoms. "One of the challenges with this study is that, among those patients whose PSA was undetectable but who got adjuvant radiation therapy, there is likely to be a certain proportion whose PSA would never have risen. Still others may have had residual disease that was just subclinical at the time they received ART."

The team applied a sensitivity analysis, which demonstrated that as long as no more than 56 percent of the patients would have been cured by the surgery alone, ART has a net-positive benefit. With two-thirds of men having no postprostatectomy recurrence, this still leaves enough gray area to warrant individual evaluation and dialogue before recommending either approach.

Impact on physician recommendations

With ESRT, patients who would never have had a recurrence avoid unnecessary treatment. However, with pre-emptive ART, the radiation dose is usually slightly lower than with ESRT, and for patients who would have had a recurrence, ART improves their odds for a cancer-free future.

Reference

1. Hwang WL, Tendulkar RD, Niemierko A, et al. Comparison between adjuvant and early-salvage postprostatectomy radiotherapy for prostate cancer with adverse pathological features. *JAMA Oncol*. 2018;4(5):e175230.

"We also have to consider factors like the patient's life expectancy, quality of life and baseline urinary, bowel and sexual function and how our treatment may impact all those things," Dr. Tendulkar continues. "In terms of tumor factors, we have to look at PSA kinetics. If someone is elderly and experiencing a very slow rise in PSA, for example, there is a good chance treatment would not be of benefit. However, for a young person with a lot of high-risk features, ART may give him the best chance of potential long-term cure."

Prospective trials needed to impact standards of care

American Urological Association guidelines recommend that *"Patients with adverse pathologic findings … should be informed that adjuvant radiotherapy, compared to radical prostatectomy only, reduces the risk of biochemical (PSA) recurrence, local recurrence and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy on subsequent metastases and overall survival is less clear."*

Although this study helps resolve contradictions that inform this recommendation, Dr. Tendulkar does not anticipate a change in the standards of care, pending the outcomes of long-term prospective, randomized trials.

Until these outcomes are known, Dr. Tendulkar's research offers data to inform more meaningful patient-physician discussions. He concludes, "Our work contributes value to the literature because of its large size and data from multiple top-notch academic centers. It also provides useful data to inform patients that perhaps ART can result in really good outcomes, while still acknowledging the risk that we may overtreat patients who may never have had a recurrence."

Save THE DATE

CONTINUING MEDICAL EDUCATION

For a full list of CME events, please visit ccfcme.org.

Oct. 15-19, 2018
Leksell Gamma Knife® Icon Course
Cleveland Clinic Gamma Knife Center
Cleveland, OH
clevelandclinicmeded.com/live/courses/radiosurgery

Oct. 26-27, 2018
5th Annual Multidisciplinary Colorectal Oncology Course
Naples Grande Beach Resort
Naples, FL
ccfcme.org/colorectal18

Nov. 8, 2018
Multidisciplinary Genitourinary Oncology Course: Focus on Prostate Cancer
InterContinental Hotel
Cleveland, OH
For information, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

Dec. 3-7, 2018
Leksell Gamma Knife Icon Course
Cleveland Clinic Gamma Knife Center
Cleveland, OH
clevelandclinicmeded.com/live/courses/radiosurgery

Dec. 8, 2018
Best of Radiation Oncology 2018
Crowne Plaza
Independence, OH
For information, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

March 8-9, 2019
2019 Multidisciplinary Head and Neck Cancer Update
Marriott Harbor Beach Resort
Fort Lauderdale, FL
For information, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

TUMOR BOARD SERIES

Complimentary CME-certified webcasts offering expert opinions and discussion based on case presentations of patients seen at Cleveland Clinic Cancer Center.
ccfcme.org/tumorboardseries

SPEAKERS BUREAU

Cleveland Clinic Cancer Center Speakers Bureau offers presentations from leading experts on a full range of oncology topics. Educational sessions are available to physicians, nurses and other healthcare professionals. Experts in hematology, medical oncology, radiation oncology, blood and marrow transplant, palliative medicine, and translational hematology and oncology research are available. Recent topics have included management of late effects of cancer treatment, circulating tumor cells and renal cell carcinoma advancements. To customize a speaker's program for your organization's specific needs or to learn more, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

In Brain Tumor Therapeutics, Options for Bypassing the Blood-Brain Barrier Are Burgeoning

No current treatments for primary brain tumors achieve significant, direct bloodstream access to the brain. Cleveland Clinic is involved in a broad range of trials aiming to change that.

Dr. Vogelbaum is Associate Director of Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

He can be reached at vogelbm@ccf.org or 216.636.0007.

For brain tumor researchers, the blood-brain barrier is a barrier in more ways than one: Not only does it prevent most therapeutics — particularly anticancer agents — from reaching the brain, but it also has been the dominant barrier to significant progress in treating primary brain tumors.

"Of the very few tools we have to treat primary brain tumors — surgery, radiation therapy and tumor-treating fields — most don't require direct bloodstream access to the brain," says Cleveland Clinic neurosurgeon Michael A. Vogelbaum, MD, PhD. The remaining tools, he adds, are a limited number of chemotherapies, and the most effective of those, temozolomide, crosses the blood-brain barrier at only about 40 percent of its systemic concentration.

"This is why we have made very little progress in treating primary brain tumors for decades now," notes Dr. Vogelbaum, Associate Director of Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

Delivering drugs directly to the brain

Impatience with the challenges posed by the blood-brain barrier has prompted Dr. Vogelbaum and his Cleveland Clinic colleagues to develop what is likely the nation's broadest offering of clinical trials of therapies designed to deliver medications directly to the brain to treat primary brain tumors.

"The general strategy of direct therapeutic delivery to the brain was validated more than two decades ago with the approval of Gliadel® Wafers for brain tumor treatment," explains Dr. Vogelbaum. "While that therapy is no longer in widespread use, it demonstrated the benefit of delivery directly to brain tissue, and a number of attempts are underway to build on that via a variety of approaches."

Those approaches fall into several categories:

- Injecting a therapeutic directly into the brain during brain tumor resection
- Slow delivery of a therapeutic into the brain over hours or days via a convection-enhanced delivery (CED) or cannula device
- Delivery of a therapeutic to the brain through the spinal fluid

Dr. Vogelbaum notes that delivery via spinal fluid has been difficult and disappointing in the setting of primary brain tumors, but the other two categories of direct delivery have shown promise in various stages of human testing. "These approaches are gaining traction, and Cleveland Clinic has developed broad and deep expertise in this area," he says. To illustrate, he outlines a number of ongoing clinical trials in which Cleveland Clinic is participating.

Direct injection in the Toca 5 Trial

This multicenter, phase 2/3 study is evaluating direct injection of the viral vector Toca 511 into the tumor resection cavity of patients undergoing surgical resection for recurrent high-grade glioma. This experimental agent is designed to infect tumor cells and make them more sensitive to Toca FC, an extended-release formulation of flucytosine that is given orally starting several weeks after resection. Patients are being randomized in open-label fashion to either this experimental

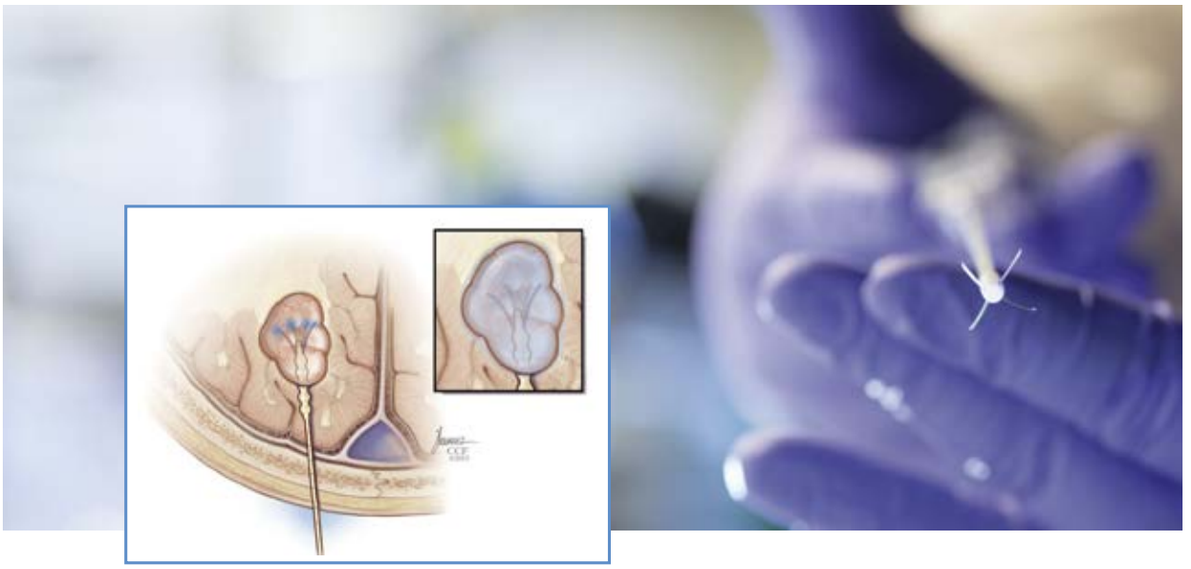


Figure. Four-port CED device. **Inset.** The infusion of a tumor using the CMC.

treatment or the standard of care (resection followed by lomustine, temozolomide or bevacizumab).

Target enrollment is 380 patients. Cleveland Clinic was one of the initial three enrolling sites. "The fact that this therapy has reached phase 3 studies is quite promising for a brain tumor therapeutic," Dr. Vogelbaum says.

Convection-enhanced delivery of the targeted toxin MDNA55

The rest of the ongoing direct delivery trials involve administration via CED or cannula devices, each from a different manufacturer. The first is a single-arm phase 2 study of MDNA55, a fusion protein comprising a genetically engineered interleukin-4 linked to a modified form of the potent cell-killing compound *Pseudomonas aeruginosa* exotoxin A. "This targeted toxin couldn't be administered any other way than by direct delivery," says Dr. Vogelbaum. "If given systemically, it would irreversibly damage the liver."

The study population is adults with recurrent or progressive glioblastoma; target enrollment is 52 patients. Cleveland Clinic is one of approximately 10 participating centers.

Cannula delivery of the oncolytic adenovirus DNX-2401

DNX-2401 is an oncolytic adenovirus designed to cause brain tumor cells to destroy themselves. It's delivered intratumorally with use of a reflux-resistant cannula and is being studied in combination with the immune checkpoint inhibitor pembrolizumab in a single-arm phase 2 trial known as CAPTIVE. Cleveland Clinic is one of about a dozen centers participating in the study, which aims to enroll 48 adults with recurrent glioblastoma or gliosarcoma.

Convection-enhanced delivery of topotecan

Cleveland Clinic is conducting a single-center pilot study of the delivery of the chemotherapy agent topotecan to tumor-infiltrated brain via the Cleveland Multiport Catheter (CMC), a four-port CED device developed at Cleveland Clinic by a team led by Dr. Vogelbaum (Figure).

The study aims to enroll 18 patients with recurrent high-grade glioma. As Dr. Vogelbaum reported at a November 2017 meeting of the Society for Neuro-Oncology, results from the trial's first 12 patients show that the CMC conveys high volumes of topotecan to both enhancing and nonenhancing tumor regions.

The company that is commercializing the CMC is now exploring using the device to deliver other brain tumor therapies in additional clinical trials.

A focus on treatment monitoring

Dr. Vogelbaum notes that in all of these studies, Cleveland Clinic researchers are focusing on the delivery of treatment to the brain tissue as well as on monitoring the penetration of therapies and their biological effects. "We coinfuse gadolinium or other tracers to observe exactly where the injected therapy is going — and where it isn't reaching," he says. "We do this in our own CED trials, and we are one of only two centers that did this early in the clinical development of Toca 511."

He adds that his team's monitoring of treatment effects is crucial to accelerating progress. "If we look at treated tumor tissue and find that it's not being impacted biologically, we can either modify the treatment early in the course of development or abandon it," he says. "This is the type of flexible and broad approach that's needed if we are to make long-overdue treatment progress against primary brain tumors. Cleveland Clinic is excited to be offering such a wide range of options to patients interested in direct therapeutic delivery."

Dr. Vogelbaum is one of the inventors of the CMC and leads the Cleveland Clinic team testing the device. He is founder and chief medical officer of Infuseon Therapeutics Inc., a Cleveland Clinic-owned spinoff company that is funding clinical development of the CMC. His roles in this development effort are covered under a Cleveland Clinic-approved conflict-of-interest management plan.

The Prognostic Potential of **Optoacoustic Imaging** in Patients with Breast Cancer

A new imaging modality may offer a wealth of prognostic information on tumor behavior and differentiation of cancer subtypes

Dr. Grobmyer is the Lula Zapis Endowed Chair to Support Breast Cancer Research and Director of Breast Surgical Oncology at Cleveland Clinic Cancer Center.

He can be reached at grobmys@ccf.org or 216.636.2843.

On Twitter: @grobmys

Optoacoustic imaging (OA), an exciting new means of illuminating vascular properties of tumors and surrounding tissues, promises to be a clinical staple for evaluation and management of patients with breast cancer. Currently in the FDA premarket process, OA technology offers the sensitivity of ultrasound imaging and the specificity of light imaging, rendering it a unique means of noninvasively assessing masses before or in lieu of biopsy. Ultimately, it may also provide a wealth of prognostic information on tumor behavior, such as aggressiveness and probability and timing of metastasis.

OA employs functional optic and real-time acoustic visibility to provide this rich store of visual evidence and data. Stephen Grobmyer, MD, Director of Surgical Oncology at Cleveland Clinic Cancer Center, explains that current imaging technology "essentially just determines the existence of a lump." With OA imaging, "the physician scans the tumor area from different angles, from which he gleans real-time information about tumor physiology." The captured cine-loop elucidates the vascularity outside the tumor as well as inside, enabling visibility into the orientation of the blood vessels and the oxygenation and deoxygenation of the blood (Figure).

"Instead of just looking at tumor cells through a microscope, with OA we can evaluate information about the tumor morphology and physiology that was never before accessible to us. Examining this morphology of the tumor, versus just the tumor cells themselves, may prove to be highly prognostic," says Dr. Grobmyer.

Changing the landscape for biopsy

OA imaging may also challenge the traditional biopsy as the post-screening next step in diagnosis. Fully 75 percent of biopsies are benign. Yet a study of over 2,000 cases, shared at the 2017 Radiological Society of North America conference, demonstrated that negative biopsies could be cut by about half if OA were used to examine the tumor.[1] Dr. Grobmyer foresees procedural benefits for patients and physicians alike. "With OA, we can potentially avoid putting our patients through the discomfort of breast biopsy, the scarring from the biopsy and the anxiety associated with waiting for results."

Differentiation of breast cancer subtypes in three of six potential pairings

Dr. Grobmyer coauthored a study[2] using the Imagio® OA/US breast imaging system that supports OA's viability as a differentiator between some tumor types. The study's aim was to determine the relationship between OA attributes and pathologically determined prognostic markers (PDPM) in the four primary types of malignant tumors: luminal A (LA), luminal B (LB), human epidermal growth factor receptor 2 (*HER2*) and triple negative (TN).

In this study, independent breast pathologists used images from the Imagio OA/US at 22 clinical sites to

References

1. Neuschler EI, Butler R, Young CA, Barke LD, Bertrand ML, Böhm-Vélez M, Destounis S, Donlan P, Grobmyer SR, et al. A pivotal study of optoacoustic imaging to diagnose benign and malignant breast masses: a new evaluation tool for radiologists. *Radiology*. 2018;287(2):398-412.

2. Grobmyer SR, Butler R, Neuschler EI, et al. Opto-acoustic imaging of breast masses: Correlation with breast biopsy prognostic indicators [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5-9; San Antonio, TX. Philadelphia (PA): AACR; *Cancer Res* 2018;78(4 Suppl):Abstract nr P5-02-04.

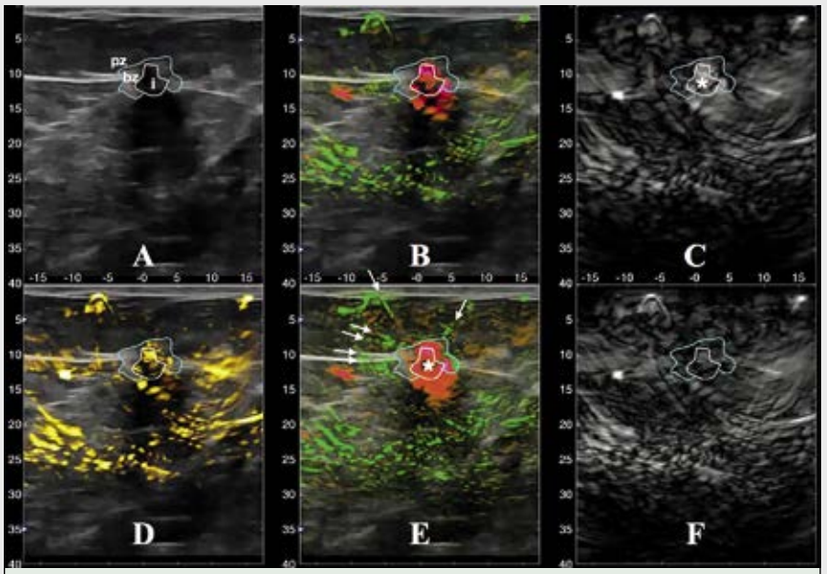


Figure. A 6-mm grade II invasive mixed ductal and lobular carcinoma, luminal B type, seen on a standard 6-on-1 OA format.

A. Grayscale image.

B. The OA combined map shows relatively oxygenated blood as green and relatively deoxygenated blood as red and is subjected to a threshold to minimize colorization of surrounding tissues.

C. The OA short-wave gray map, which shows relatively more deoxygenated hemoglobin.

D. The OA total hemoglobin map, where oxygenated blood is not distinguished from deoxygenated blood and total hemoglobin is shown with yellow and is also subjected to a threshold.

E. The OA relative map shows oxygenated blood in green and relatively deoxygenated blood in red and is not subjected to a threshold.

F. The OA long-wave gray map, which shows relatively oxygenated blood more.

Segmentation lines were manually drawn on the ultrasound image and propagated to coregistered locations on the five OA maps to help distinguish distribution of OA findings within three zones:

iz = internal zone, corresponding to the hypoechoic central nidus of the mass;

bz = boundary zone, corresponding to the ill-defined echogenic halo that occurs around most invasive masses; and

pz = peripheral zone, which lies peripheral to the boundary zone.

This small 6-mm luminal B carcinoma is positive in all three zones. There are polymorphic deoxygenated vessels within the internal zone, there is a deoxygenated blush within the boundary zone between the white and aqua segmentation lines, and there are multiple oxygenated peripheral radiating arteries within the peripheral zone (arrows). Note that the red deoxygenated blush is better seen on the OA shortwave map.

The OA feature scores assigned were 5 for the internal vessel score, 5 for internal blush score, 3 for internal total hemoglobin score, 6 for boundary zone deoxygenated blush score and 5 for peripheral zone radiating vessel score. The unweighted sum of all five OA feature scores was 24 of 26. The weighted sum of scores predicted a risk of malignancy of 97 to 99 percent.

Image and figure republished with permission from Neuschler EI, Butler R, Young CA, Barke LD, Bertrand ML, Böhm-Vélez M, Destounis S, Donlan P, Grobmyer SR, et al. A pivotal study of optoacoustic imaging to diagnose benign and malignant breast masses: a new evaluation tool for radiologists. *Radiology.* 2018;287(2):398-412.

score internal (nidus) and external (boundary and periphery) features of 655 invasive and 22 DCIS tumors. These scores were then reviewed by an experienced central breast pathologist blinded to the OA assessment. Identification of tumor ER, PR and *HER2*-neu expression was performed through immunohistochemistry.

Dr. Grobmyer's team conducted a two-way analysis of variance (ANOVA) and Tukey HSD (honest significant difference) tests for pairwise comparisons. All statistical testing was done at a 5 percent significance level.

Findings of significant correlations with PDPM were robust between three of the six possible pairings: LA and LB, LA and *HER2,* and LA and TN. LA tumors are the common denominator in these findings. There were no significant correlations between the PDPM and scorers' assessments in the comparisons of LB and *HER2,* LB and TN, or TN and *HER2*.

Fertile ground for clinical application and further research

From the results of this study and other research conducted to date, Dr. Grobmyer expects clinicians and researchers will quickly recognize the potential of this safe, painless and real-time imaging. "I suspect we are in the infancy of this technology. But as the value of visualizing and describing tumor vascularity becomes recognized for both diagnosis and treatment, I believe OA has the potential to really change how we approach the care of patients." He continues, "There is no precedent for an imaging technology that discriminates between various kinds of breast cancer. And that capability may just be the tip of the iceberg."

New $2.6 Million Grant to Develop Novel Disease Models of Colorectal Cancer

Emina Huang, MD, of the departments of Colorectal Surgery and Stem Cell Biology and Regenerative Medicine, has been awarded a collaborative five-year, $2.6 million grant from the National Cancer Institute (NCI) to create innovative models of colorectal cancer (CRC) that will enhance understanding of how the disease develops and spreads.

This grant — a collaboration between Cleveland Clinic, Duke University and Cornell University — is the newest project funded by NCI's Cancer Tissue Engineering Collaborative (TEC) Research Program. The program supports the development and characterization of advanced tissue-engineered technologies for cancer research. Only four other research institutions nationwide are TEC-funded: Boston University, Harvard University, Brigham and Women's Hospital and Massachusetts Institute of Technology.

Leading-edge models of colorectal cancer

Dr. Huang and her team will work to develop three leading-edge models of CRC that will help researchers uncover the role inflammation, messenger RNA (transcriptome) and epigenetics play in the metastasis of CRC. These models are unique because they will all use human tissues, both from the colon and from other sites throughout the body. Studying CRC using cells from people, the population of ultimate interest, will maximize the applicability of findings and may speed the time to discovery.

This project is also innovative in that other conditions aside from CRC — including hypoxia and altered glucose levels — are reflected in these models. This will help mimic the extreme complexity of the CRC microenvironment. Additionally, the models are scalable and will allow for comparison between various cell types and combinations within and among the three models.

A collaborative effort

While Dr. Huang is the principal investigator for the project, each collaborating organization will take the lead on developing one of the three models. Dr. Huang's lab will develop an organotypic model. They will remove native cells from human colons, taken from resected colons and cancerous lesions, and repopulate them with new cells, including healthy cells as well as various types of cancer cells. Studying how the different classes of cells respond will help researchers understand the roles inflammation and cellular invasion and differentiation play in metastasis.

Dr. Huang codirects Lerner Research Institute's Center of Excellence in Colon Cancer Metastasis Research. This program brings together top scientists with frontline physicians to speed the translation of lab discoveries into real benefits for patients. The center is currently working on several projects, including examining colon cancer's cellular microenvironment, reversing the effects of angiogenesis, and understanding how genetic changes may make colon cancer cells more aggressive in some individuals and how those changes may be reversed. This project is the newest addition to the center's impressive portfolio.

POEMS Five-Year Data Show Goserelin + Chemotherapy Helps Women with Breast Cancer Safely Preserve Fertility

Women undergoing chemotherapy for breast cancer and other malignancies face a serious risk of ovarian toxicity, which can lead to premature menopause. This complication is especially concerning to patients of child-bearing age who wish to preserve their fertility.

"It's particularly an issue for breast cancer patients," says Halle Moore, MD, staff in the Department of Solid Tumor Oncology. "We're a little reluctant to give hormone replacement therapy to them — which would ordinarily help with premature menopausal symptoms — even if they don't have hormone-sensitive breast cancer."

In 2015, Dr. Moore and colleagues published in the *New England Journal of Medicine* the results of the Prevention of Early Menopause Study (POEMS), a phase 3 clinical trial developed to assess whether ovarian failure could be prevented by temporarily suppressing ovarian function by including goserelin, a gonadotropin hormone-releasing hormone (GnRH) agonist, with standard chemotherapy.

"We showed that goserelin use reduced the risk of ovarian failure by about 70 percent in our population," Dr. Moore says.

Now, Dr. Moore has five-year follow-up results that continue to show that patients who receive both goserelin and chemotherapy are more likely to have successful pregnancies and perhaps even to live longer than those who don't.

Five-year follow-up data

With a median follow-up of 5.1 years, Dr. Moore and her colleagues found that 22 percent of patients in the goserelin group had at least one pregnancy compared with 12 percent in the standard group (OR 2.38; 95% CI, 1.08-5.26; $P = 0.03$).

They also found that disease-free survival estimates were 88 percent in the goserelin arm compared with 79 percent in the standard arm (HR = 0.50, $P = 0.05$), and five-year overall survival was 92 percent with goserelin versus 83 percent in the standard arm (HR = 0.47, $P = 0.06$).

"With long-term follow-up, our data continue to show that women were significantly more likely to become pregnant if they used the goserelin," Dr. Moore says, "and that they were more likely to be alive and free of their cancer."

Mutations in Aplastic Anemia Can Predict Increased Risk of Myelodysplastic Syndromes

Dr. Maciejewski is Chair of the Department of Translational Hematology and Oncology Research and recipient of the National Cancer Institute's Outstanding Investigator Award.

He can be reached at maciejj@ccf.org or 216.445.5962.

Not all mutations are prognosticative

Aplastic anemia (AA) is a rare condition that occurs when bone marrow and its hematopoietic stem cells become damaged and fail to produce new blood cells. In this disease, the body's immune system attacks the stem cells and leads to bone marrow failure, which causes fatigue, prolonged bleeding from cuts, recurrent infections and other symptoms due to low blood counts.

The condition is treatable about 70 percent of the time, but a small number of patients with AA develop clonal complications that can lead to myelodysplastic syndromes (MDS), which can then lead to acute myeloid leukemia.

Investigators have been searching for decades for particular genetic mutations that might predict which patients with AA will develop MDS. Now Cleveland Clinic researchers have discovered some of these genetic seeds of future MDS using next-generation sequencing and inherent molecular diagnostics. They published their results in *Blood*.

"We found that mutations, which serve as seeds of future complications — the evolution to malignant conditions — can be traced very early on in the disease," says Jaroslaw P. Maciejewski, MD, PhD, Chair of the Department of Translational Hematology and Oncology Research and senior author on the paper. "But only mutations in specific genes convey this risk of evolution."

Some mutations come and go

In order to determine which mutations might be predictive of later MDS development, Dr. Maciejewski and his coauthors collected bone marrow and/or blood samples from 258 Cleveland Clinic patients with AA and 59 patients with paroxysmal nocturnal hemoglobinuria, another complication of AA. Among those patients, 35 progressed to secondary MDS. For comparison, they also assembled a cohort of 853 patients with primary MDS.

The researchers found that some mutations appeared and disappeared during the course of the disease. "Only certain mutations persist from AA to MDS, while other mutational events might come and go without seemingly predicting future risk," Dr. Maciejewski says. "And the ones that don't convey the risk merely represent the damage to the stem cell compartment and how few stem cells are left in the marrow of aplastic anemia." For instance, the analysis found a mutation of the gene *DNMT3A* occurred in some patients with AA but was absent in patients with post-AA MDS.

Dr. Maciejewski and his coauthors also serially analyzed a cohort of 21 AA cases that progressed to MDS and 13 that did not. They found more mutations of the genes *ASXL1, U2AF1* and *JAK2* in progressors than in those who remained stable, which suggests that certain clonal events in the MDS stage of the disease were indeed acquired early at presentation of AA and that some early events may lead to subsequent clonal evolution.

Predictive mutations mean shorter survival

Finally, they found shorter median progression-free survival (two years) and overall survival (2.6 years) among patients with MDS-driver mutations at presentation of AA compared with cases without these somatic alterations.

Dr. Maciejewski says the next step is to develop diagnostic procedures and validate them so that the identification of certain mutations could lead to therapeutic consequences such as the decision to proceed to bone marrow transplant or to avoid certain drugs. "If I could predict which patients with AA would develop MDS," he says, "I would treat them so that these clonal cascades that lead to MDS did not occur."

A **New Biomarker** for Guiding Prostate Cancer Treatment

One step closer to identifying patients predisposed to treatment-resistant prostate cancer

Back-to-back discoveries demonstrate for the first time how a testosterone-related genetic abnormality can help predict individual patient responses to specific prostate cancer therapies.

The studies, published in *JAMA Oncology*, suggest that men who inherit this variant would benefit from a personalized treatment plan that targets specific hormonal pathways.

Led by Nima Sharifi, MD, Co-Director of Cleveland Clinic's Center of Excellence for Prostate Cancer Research, the research teams studied the role of the *HSD3B1*(1245C) genetic variant in two different prostate cancer patient populations, following androgen deprivation therapy (ADT). In 2013, Dr. Sharifi discovered that prostate cancer cells with the genetic abnormality survive ADT by producing their own androgens.

In the first study,[1] Dr. Sharifi and colleagues from Memorial Sloan Kettering Cancer Center, Harvard/Dana Farber Cancer Institute and University of Michigan Comprehensive Cancer Center analyzed 213 men whose prostate cancer recurred after radiation therapy and who underwent ADT. They found for the first time that following radiation and ADT, prostate cancer was much more likely to spread — and spread rapidly — in men who had the *HSD3B1*(1245C) variant.

The second study,[2] a collaboration with researchers at University of California San Francisco, focused on 90 men with metastatic cancer who had become resistant to ADT. They were subsequently treated with ketoconazole, which blocks production of androgens outside of the testes (e.g., those developed by prostate cancer cells that are evading ADT treatment).

Surprisingly, men with the genetic anomaly fared better on ketoconazole than men without the variant. This finding raises the possibility that targeting variant tumors' backup androgen supply (outside of the testes) could be a successful strategy when ADT fails.

"We hypothesized that *HSD3B1*(1245C) variant tumors become resistant to ADT because they have a backup supply of androgens," says Dr. Sharifi. "However, relying on these extragonadal androgens makes them more sensitive to ketoconazole."

These discoveries complement earlier studies and support the use of *HSD3B1*(1245C) as a predictive biomarker to help guide critical treatment decisions. While the outlook for patients with this gene variant is poor, these studies offer hope for a new treatment strategy for these men. More studies are needed using next-generation androgen inhibitors, such as abiraterone and enzalutamide, Dr. Sharifi emphasizes.

"We are hopeful that these findings will lead to more personalized and effective treatments for prostate cancer," says Dr. Sharifi. "If men carry a specific testosterone-related genetic abnormality, we may be able to personalize their therapy and treat specific patients more aggressively."

This work was supported by the U.S. Department of Defense, Howard Hughes Medical Institute, Prostate Cancer Foundation, American Cancer Society, the U.S. Army Medical Research and Materiel Command, and grants from the National Cancer Institute.

Dr. Sharifi holds the Kendrick Family Chair for Prostate Cancer Research and co-directs Cleveland Clinic's Center of Excellence for Prostate Cancer Research.

He can be reached at sharifn@ccf.org or 216.445.9750.

On Twitter: @NimaSharifiMD

References

1. Hearn JWD, Xie W, Nakabayashi M, Almassi N, Reichard CA, Pomerantz M, Kantoff PW, Sharifi N. Association of *HSD3B1* genotype with response to androgen-deprivation therapy for biochemical recurrence after radiotherapy for localized prostate cancer. *JAMA Oncol*. 2018;4(4):558-562.
2. Almassi N, Reichard C, Li J, Russell C, Perry J, Ryan CJ, Friedlander T, Sharifi N. *HSD3B1* and response to a nonsteroidal *CYP17A1* inhibitor in castration-resistant prostate cancer. *JAMA Oncol*. 2018;4(4):554-557.

By Brian Bolwell, MD

Dr. Bolwell is Chairman of Taussig Cancer Institute, Cleveland Clinic Cancer Center.

He can be reached at bolwellb@ccf.org or 216.444.6922.

On Twitter: @brianbolwellmd

Cancer Programming and **Clinical Alignment**

As a large cancer center, one of our challenges is clinical alignment among our numerous locations. We have many regional clinics and hospitals that deliver cancer care — how do we promote one clinical standard of care?

Two words: cancer programming.

Each cancer program is a disease-based team composed of physicians from different specialties as well as nurses and other support staff. Team-based care for each cancer diagnosis is critical. Programming allows us to prioritize and structure different aspects of team-based care, including multidisciplinary clinics, tumor boards, care paths and reduction in time to treat. These elements are tracked on scorecards, and each program is accountable to an executive committee for its results. We devote resources such as program managers and patient navigators to each program.

Three elements are especially key to the success of cancer programming:

Care paths. Care paths are evidence-based algorithms that define the most effective and efficient treatment in a specific clinical situation, and are especially complex in our field given the highly individualized nature of the disease. There are three main criteria we consider when developing care paths: efficacy, toxicity and cost. When we develop care paths for a given situation, we involve physicians from our main academic campus and from our regional locations. Care paths are available to purchase from outside vendors, but we believe that internal development of care paths promotes teamwork and a sense of ownership, leading to better participation and regional integration.

Tumor boards. Tumor boards allow experts to review a complex case and work together to develop and refine therapeutic strategy. In each case, we discuss any applicable care paths as a part of the overall process to elevate the standard of care. We ensure that our tumor boards are accessible to physicians at all locations and that physicians outside of the main campus have opportunities to present their cases at both regional and overall program tumor boards. We make tumor board participation a criterion for "membership" in our cancer center, so the meetings also function as an alignment tool for our community surgeons.

Access. Access is of profound importance to cancer patients. Every patient upon initial diagnosis is filled with fear and anxiety. The sooner we see and develop a treatment plan for a patient, the better it is for everyone. Our cancer programs have made reducing time to treat (TTT) — days between diagnosis of cancer and first treatment — a priority. Our study of 3.7 million patient records shows that prolonged TTT is highest among academic cancer centers and appears to be worsening annually. Our overall TTT initially was similar to that of other major cancer centers, but we have reduced it from 39 days to 29 days, with our largest cancer programs (breast, colorectal and lung) showing the greatest reduction. We want to keep going and reduce TTT to less than 20 days. Our work on reducing TTT promotes access, multidisciplinary care development and regional alignment; lowers patient fear and anxiety; and elevates our culture.

Clinical integration of regional assets is important and requires significant effort. We believe that developing disease-based programs and working on shared initiatives such as the development of care paths; encouraging robust regional tumor board participation; and reducing time to treatment has allowed us to achieve successful clinical integration of our diverse repertoire of assets.

Affiliating with Cleveland Clinic Cancer Center

An affiliation with Cleveland Clinic Cancer Center means connecting your physicians and patients with the most advanced care and distinguishing your cancer program as a market leader. It means strength and flexibility in a time of uncertainty. It means creating value across your enterprise while retaining the culture and values that distinguish your organization.

It means bringing the future of cancer care to your community.

To learn how Cleveland Clinic Cancer Center can help your organization execute optimal cancer therapy in a value-based care environment, call 216.445.4399 or visit clevelandclinic.org/canceraffiliates.

Search Our Cancer Clinical Trials Database

Stay up to date on Cleveland Clinic's more than 200 active clinical trials for cancer patients.

Search a database of open clinical trials by disease, phase, physician or location.

Browse real-time information on each trial's objective, eligibility criteria, phase(s) and more.

Connect to our Cancer Answer Line for more information about a trial or to enroll patients.

To search the database, go to clevelandclinic.org/cancerclinicaltrials

VELOSANO

100% supports lifesaving cancer research at Cleveland Clinic

In its four-year history, VeloSano has raised $12.4 million.

The cycling event, which takes place in and around Cleveland each July, allows individuals and teams ranging from casual riders to avid cyclists and virtual participants to pedal sponsored rides of 12 to more than 200 miles over two days. One hundred percent of the funds collected is applied to cancer research projects, laboratory expenses and personnel recruitment at Cleveland Clinic Cancer Center.

A $1 million donation from Cleveland Clinic Trustee Steward A. Kohl and his wife, Donna, established VeloSano in 2013. The couple were veterans of the Pan-Mass Challenge, a Massachusetts cancer bike-a-thon, and had seen the impact it had on riders, the community and collective efforts to fight cancer.

Proceeds from the event are distributed in two ways:

- **VeloSano Pilot Awards** provide seed funding for cancer research activities across the Cleveland Clinic enterprise. Utilizing a competitive application and peer-review selection process, the Pilot Awards support projects with a high likelihood of obtaining future extramural funding. The focus of these one-year grants is to build on and transition recent advancements in cancer genetics, epigenetics and basic and translational tumor immunology.
- **VeloSano Impact Awards** are distributed by the event's Medical Chairman, Brian J. Bolwell, MD, FACP, to satisfy the critical needs of Cleveland Clinic Cancer Center. Impact Awards address strategic priorities that will advance investigational abilities in cancer research and ensure that caregivers and patients have access to the best medical talent and technology available.

Sixteen Pilot Awards and Eight Impact Awards were allocated using 2017 VeloSano funds:

Pilot Awards

Clonal composition governs the susceptibility of *BRAF* mutant cancers to therapy
Mohamed Abazeed, MD, PhD

Targeting fatty acid desaturase 1 (FADS1)-derived lipid mediator signaling in hepatocellular carcinoma
Mark Brown, PhD

Microglial regulation of sex-specific differences in glioblastoma
Dimitrios Davalos, PhD

Breath analysis and the microbiome in gastrointestinal graft-versus-host disease
Betty Hamilton, MD

Targeting chromatin modifier gene mutations in urothelial carcinoma using synthetic lethality
Byron Lee, MD, PhD

Holographic visualization for performance of percutaneous ablation of solid tumors
Charles Martin, MD

Overcoming suppression of immune cell function by glioblastoma isocitrate dehydrogenase mutation
Thomas McIntyre, PhD

Prospective validation and functional characterization of a gene expression signature for identification and risk stratification of small-cell (neuronal type) bladder cancer
Omar Mian, MD, PhD

Chemosensitizing endometrioid tumors with LCK inhibitors
Ofer Reizes, PhD

Construction of morbidostat mammalian cells to study temporal genomics during the evolution of resistance
Jacob Scott, MD

The OAS-RNASE L pathway mediates tumor cell death from 5-azacytidine treatment
Robert Silverman, PhD

Synergistic effects of interleukin-12 proinflammatory cytokine therapy with PD1 blockade
Ahmad Tarhini, MD, PhD

Establishing preclinical in vivo models of small-cell lung cancer for proof of principle of novel therapeutic modalities
Vamsidhar Velcheti, MD

Effects of synthetic-lethal compounds in models of SF-3B1 mutant myelodysplastic syndrome
Valeria Visconte, PhD

Therapeutic targeting of epigenetic modifiers in the glioblastoma perivascular niche
Michael Vogelbaum, MD, PhD

Hypoxia drives glioma stem cell migration and invasion via vasorin-TGFβ signaling
Jennifer Yu, MD, PhD

The inaugural VeloSano ride in 2014 raised nearly $2 million. VeloSano 2 raised $3 million in 2015.

VeloSano 3, in 2016, raised $3.37 million, and VeloSano 4, in 2017, raised $4.17 million.

Fundraising continues through Oct. 1 for VeloSano 5, held in July 2018.

VeloSano 6 weekend is scheduled for July 19-21, 2019.

Impact Awards

Evaluating the efficacy of a proposed 11-step, community-based interventional program to educate, assess risk and barriers, and complete colorectal screening among underserved African Americans
Samir Abraskia, MD

Biostatistics
Brian Hobbs, PhD

Colon cancer metastasis
Emina Huang, MD

Chronic myelomonocytic leukemia
Jaroslaw Maciejewski, MD, PhD

Hepatocellular carcinoma
Yogen Saunthararajah, MD

NCI early-phase therapeutic trials/ phase 2 intent consortium
Dale Shepard, MD, PhD

Using insertional mutagenesis to rapidly identify resistance mechanisms in cancer
George Stark, PhD

Defining markers of radiosensitivity: radiogenomic profiling of rhabdomyosarcoma
Stacey Zahler, DO

New Staff

Larissa Schwartzman, MD
Hematology and Oncology

Smitha Krishnamurthi, MD
Hematology and Oncology

Nausheen Ahmed, MD
Hematology and Oncology

Cancer Advances provides information from Cleveland Clinic cancer specialists about innovative research and diagnostic and management techniques.

Please direct correspondence to:
Taussig Cancer Center / CA
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Cleveland Clinic Cancer Center annually serves thousands of cancer patients. More than 450 clinicians, scientists and other cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Cleveland Clinic Cancer Center is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

***Cancer Advances* Medical Editor**
Brian I. Rini, MD, FACP
Director, Genitourinary Cancer Program

Managing Editor
Deborah Booth Summers

Designer
Amy Buskey-Wood

Photography
Russell Lee, Tom Merce, Yu Kwan Lee, Greg Mueller

Medical Illustration
Joe Kanasz, Dave Schumick

Cancer Advances is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Cleveland Clinic

The Cleveland Clinic Foundation
Cleveland Clinic Cancer Center
9500 Euclid Ave. / AC311
Cleveland, OH 44195

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2018-19

NCI CCC® A Comprehensive Cancer Center Designated by the National Cancer Institute

Case Western Reserve University | Case Comprehensive Cancer Center

NCCN National Comprehensive Cancer Network®

Stay Connected with Cleveland Clinic Cancer Center

24/7 Referrals

855.REFER.123
(855.733.3712)

clevelandclinic.org/refer123

Outcomes Data
View Outcomes books at clevelandclinic.org/outcomes.

CME Opportunities
Visit ccfcme.org for offerings from Cleveland Clinic's Center for Continuing Education.

Consult QD — Cancer
News, research and perspectives from Cleveland Clinic experts:
clevelandclinic.org/consultqdcancer

Cancer Advances eNews
Sign up to received our eNewsletter sent bi-monthly.
clevelandclinic.org/canceradvances

Facebook.com/CMEClevelandClinic

@CleClinicMD

clevelandclinic.org/MDlinkedin

clevelandclinic.org/cancer

Cleveland Clinic Cancer Center provides complete cancer care enhanced by innovative basic, genetic and translational research. It offers the most effective techniques to achieve long-term survival and improve patients' quality of life.

The Cancer Center's more than 450 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based in Taussig Cancer Institute and in Cleveland Clinic's 26 other clinical and special-expertise institutes, as well as cancer specialists at our regional hospitals, health centers and Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as a top hospital in the country (*U.S. News & World Report*), where more than 3,400 staff physicians and researchers in 140 specialties collaborate to give every patient the best outcome and experience.

18-CNR-660