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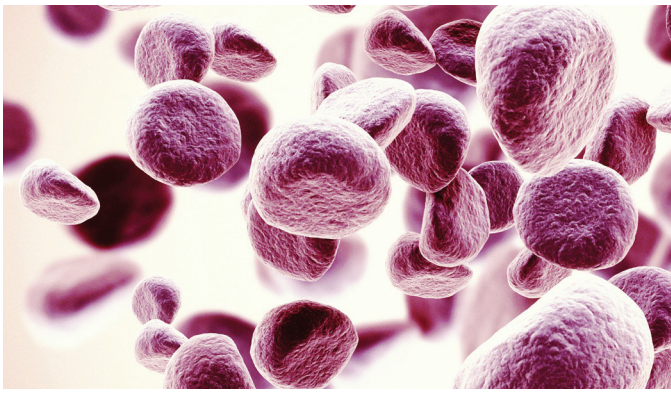
SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

INNOVATIONS IN CANCER



FALL 2015

FROM THE DIRECTOR

Initiating Investment

To achieve ever-improving outcomes for our patients requires garnering the appropriate resources. A big part of that is developing the capital base necessary to fund the development of innovative technologies and novel clinical trials that can make a difference in our patients' lives.

In this issue of Innovations in Cancer, we explore some of the investments we've made at University Hospitals Seidman Cancer Center – investments that are paying off for patients.

Our cover story features the work of our radiology and radiation oncology teams, including **Vikas Gulani, MD, PhD; Mark Griswold, PhD; Mitchell Machtay, MD; Bryan Traughber, MD; and Raymond F. Muzic Jr., PhD**. Drs. Gulani and Griswold have worked to bring a quantitative aspect to MRI. The resulting technology, dubbed "magnetic resonance fingerprinting," or MRF, is already showing promise as a new way to diagnose and treat brain and prostate cancer. At the same time, Drs. Machtay, Traughber and Muzic are working to optimize UH Seidman Cancer Center's PET/MR system – one of the first in the world to be put to clinical use. The team is employing the system in treatment planning for gynecological and gastrointestinal malignancies, as well as exploring how to develop more accurate MR-based attenuation correction (MR-AC) methods. Supported by a multiyear grant from the National Cancer Institute, this work promises to expand the use of PET/MR systems in cancer clinical trials.

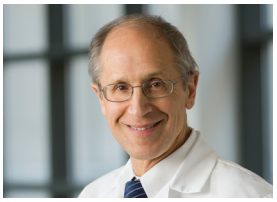
Another large investment we've made at UH Seidman Cancer Center is in our new Proton Therapy Center, scheduled to open in summer 2016 as the first in Ohio and the surrounding region. In our feature article, pediatric radiation oncologist **David Mansur, MD**, discusses how this technology will improve the precision of radiation therapy provided to our pediatric patients.

Also in radiation oncology, **Rod Ellis, MD**, is making an innovative hydrogel spacer available to prostate cancer patients, reducing the rectal radiation that can be so problematic. The technology was used for the first time in the U.S. at the UH Geauga Medical Center site of UH Seidman Cancer Center.

In cancer immunotherapy, **Julian Kim, MD**, and the team of **Marcos de Lima, MD, Alex Huang, MD, PhD, and David Wald, MD, PhD**, are exploring cellular therapies in trials made possible, in part, by donors to UH Seidman Cancer Center and the Case Comprehensive Cancer Center at Case Western Reserve University. Using activated T cells generated in a home-grown, patented process, Dr. Kim is testing their effects on patients with advanced melanoma. Similarly, Drs. de Lima, Huang and Wald are looking to natural killer (NK) cells to boost the stubbornly low survival rates for adolescent and young adults with sarcomas or acute myeloid leukemia (AML).

The articles in this issue of Innovations in Cancer cover just a few of the many investments we've made in our patients at UH Seidman Cancer Center. But they are a testament to our ongoing initiative and commitment to achieving ever-better outcomes.

Warm regards,



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Making **Natural Killers** More Lethal

Researchers exploring new NK cell approaches to leukemia, sarcoma in adolescent and young adult patients

Survival rates for the most common cancers among adolescents and young adults (AYA) remain stubbornly low, especially for acute myeloid leukemia (AML), osteosarcoma and Ewing's sarcoma.

"Unfortunately, the long-term survival for AYA patients with AML is still less than 50 percent, and there have been no standard changes in therapy in more than 40 years," says pediatric hematologist and oncologist Alex Huang, MD, PhD. "For Ewing's sarcoma, despite all the chemotherapeutics we have, survival is still in the 60 to 70 percent range. It's not a well-treated disease."

To address this unmet clinical need, Dr. Huang and collaborators from UH Seidman Cancer Center and the Case Comprehensive Cancer Center at Case Western Reserve University are looking to natural killer (NK) cells. Specifically, the team has identified a way to make these potent immunological weapons even more lethal against AYA cancers.

The researchers' work is funded as part of a $6.7 million gift from Char and Chuck Fowler to the Case Comprehensive Cancer Center, specifically earmarked for research that will lead to better treatments and cures for AYA cancers. The Fowlers lost their teenage daughter, Angie, to melanoma in 1983. Their gift to the Case Comprehensive Cancer Center represents the first-ever creation of a center focused on AYA cancer within the nation's 45 Comprehensive Cancer Centers designated by the National Cancer Institute. Additional funding for the project comes from the Marc Joseph Fund at UH Rainbow Babies & Children's Hospital and the Fellow Research Award Program of its Board of Directors.

Leading the NK research team is UH Seidman Cancer Center hematologist and oncologist Marcos de Lima, MD, who was previously at MD Anderson Cancer Center in Houston. Collaborating with MD Anderson's Dean Lee, MD, Drs. de Lima, Huang and UH pathologist David Wald, MD, are boosting NK cell expansion by using artificial antigen-presenting cells transfected with membrane-bound interleukin 21 (IL-21). The researchers believe that the IL-21 mediates telomere lengthening in the cells, avoiding the telomere shortening that often occurs with other expansion methods.

"This platform leads to massive *in vivo* expansion of NK cells, generating about 30,000 times more cells in just three weeks, thereby overcoming the problem of insufficient NK cells for infusion," Dr. de Lima says.

However, an adequate NK cell supply is only part of the story. Armed with a sufficient number of NK cells, the Angie's Institute/UH Seidman Cancer Center team is hyperactivating the cells with a new investigational agent.

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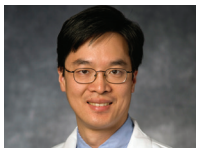

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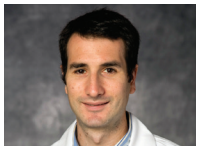

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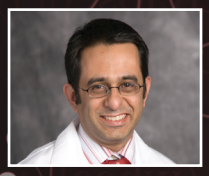
"We've developed a novel, potent and highly specific agent that inhibits the cellular protein GSK3," Dr. Wald says. "We found that pretreating the expanded NK cells with inhibitors in this class results in dramatically enhanced killing of a wide variety of AML cell lines and primary patient samples in mouse xenografts." The GSK3 inhibitor, dubbed INV 117, works by increasing the adhesion of NK cells to their cancerous target cells.

Although the work is still in the preclinical stage, the researchers say they're encouraged by its early results and potential to better serve AYA cancer patients. They are planning collaboration through a consortium with physician-scientists from the Medical College of Wisconsin, University of Wisconsin and Alberta Children's Hospital in Canada to test the new compound in a clinical trial for AYA patients with AML or Ewing's sarcoma.

"Our collaborators have existing NK cell protocols, but they don't have the functional augmentation strategies we've developed here," says Dr. Huang. "We're trying to leverage their expertise with our scientific discoveries to translate this to the AYA population faster than we could do by ourselves."

For more information on this research or other work at Angie's Institute at UH Rainbow Babies & Children's Hospital, contact **Alex.Huang@UHhospitals.org.**



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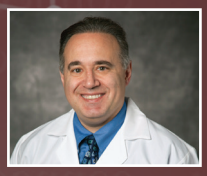

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Innovative Imaging

Emerging technologies play critical role at UH Seidman Cancer Center

"Every biopsy is an imaging failure."

For Vikas Gulani, MD, PhD, a radiologist at University Hospitals Seidman Cancer Center, those are words to live by. Collaborating with Mark Griswold, PhD, Professor of Radiology at Case Western Reserve University School of Medicine, he's working toward a day when biopsies are obsolete. Specifically, the pair is working to shift the burden of cancer diagnosis from biopsy to imaging, fusing the qualitative information available from typical MR with quantitative values for each pixel in the image.

"If you look at a typical MR image, it is a map of the anatomy and that's it," Dr. Gulani says. "The maps of the anatomy are beautiful, but they are not quantitative. What that means is that day to day, scanner to scanner, site to site, it is very difficult to compare results."

Drs. Griswold, Gulani and colleagues worked on this problem off and on for about 10 years. Just when the group reached its lowest point and was about to give up, Dr. Griswold posed an important question: What would happen if they didn't care what the image looked like?

"We decided to only go after a map of tissue properties that we care about," Dr. Gulani says. "As soon as you stop trying to collect a traditional image and go instead after the properties, then you can let your signal vary in crazy ways that you never thought possible."

The result of this insight is magnetic resonance fingerprinting (MRF) – a new imaging technology that can generate immediate and simultaneous values for T1 and T2 for each pixel in the image. These tissue characteristics describe the environment of each particular proton, such as fat or water. The signal from each pixel is matched against a "dictionary" of all possible signals, and the match yields the underlying quantitative values that went into creating the dictionary entry, even when the signal itself is really "noisy."

Dr. Gulani likens MRF to distinguishing the letter "A" from the letter "B" on a page, even when parts of the letter are faint or missing, or to being able to correctly identify "The Star-Spangled Banner" on a radio with a lot of static, just based on the words "say" and "see" and a fragment of melody.

"The pattern-matching algorithm that is your brain knows what it is," he says. "MRF works the same way."

Drs. Griswold, Gulani and colleagues first described MRF in the journal Nature in 2013. Since that time, they've demonstrated that the technology can distinguish primary from secondary brain tumors and the more aggressive glioblastoma multiforme from oligodendrogliomas.

"This speaks to the power of possibly being able to identify tumors from the scan itself," Dr. Gulani says.

Dr. Gulani and colleagues at UH Seidman Cancer Center are also employing MRF technology to improve the often-problematic diagnosis and staging of prostate cancer.

"If you look at how traditional imaging is done for the prostate, one component is diffusion mapping," he says. "The lower the apparent diffusion coefficient (ADC), the more suspicious it is for cancer in certain parts of the prostate."

By combining traditional MR with MRF, the team is able to plot values for ADC and T2 that clearly differentiate tumor from nontumor. They've also been able to distinguish high-grade from low-grade tumors using T1, T2 and ADC values. For Dr. Gulani this raises the possibility of a more evidence-based approach to active surveillance.

"Patients with low-grade tumors could be followed," he says. "In the future, perhaps if their T1 drops or ADC drops or both, then those are the people who need the follow-up biopsy. But the rest of them can possibly just be watched."

UH Seidman Cancer Center an early adopter of PET/MR

Innovations in imaging at UH Seidman Cancer Center are not limited to MRF. In fact, the radiation oncology and radiology teams here are among the first in the world to employ a PET/MR system, putting it to immediate clinical use according to the vision of Pablo Ros, MD, Radiology Department Chair.

"The combination of MR and PET is a quantum leap above CT-based radiation therapy planning," says Mitchell Machtay, MD, Chairman of Radiation Oncology.

"PET/MR leverages the excellent soft-tissue contrast and functional sequences of MR with the molecular information of PET in one single, hybrid imaging technology," adds Raymond F. Muzic Jr., PhD, Professor of Radiology at Case Western Reserve University School of Medicine and a clinical researcher at UH.

At UH Seidman Cancer Center, the radiation oncology team was one of the first to use the system clinically for radiation therapy planning in gynecologic and gastrointestinal malignancies. A research effort is also underway focused on using PET/MR for adaptive radiotherapy planning in patients with lung cancer.

"Patients often start with very large lung cancers," says Bryan Traughber, MD, a radiation oncologist at UH Seidman Cancer Center. "We're exploring using PET/MR imaging during the course of treatment to decrease the field size, adapt the radiation plan and thereby decrease radiation to normal tissues, while maximizing radiation delivery to the tumor."

"PET is very helpful, but the standard tracer, FDG, is taken up by inflammatory cells, making it difficult to differentiate between radiation-induced inflammation and residual cancer," Dr. Traughber adds. "However, by combining multiple data sets including FDG-PET and MR perfusion and diffusion, then you can more reliably distinguish between inflammation and residual tumor compared to any single modality alone. I think PET/MR could be a very powerful tool for treatment planning and replanning of patients with lung cancer."

Drs. Muzic and Traughber, joined by Dr. Melanie Kotys, Director of Philips MR R&D in North America, are leading an academic-industry collaboration of physicians, physicists and engineers from UH, Case Western Reserve University and Philips Healthcare to develop more accurate MR-based attenuation correction (MR-AC) methods for PET/MR systems. The project is supported by a multiyear grant from the National Cancer Institute (NCI).

"In order to utilize PET/MR in a clinical trial setting, images must be quantitatively accurate and reproducible across patients and institutions," Dr. Muzic says. "A specific challenge is accounting for a sufficient number of tissue types, particularly differentiating bone from air. While bone and air have dramatic differences in the degree to which they attenuate PET photons, they both have a signal level comparable to that of noise when using conventional MR pulse sequences. Consequently, current MR-AC methods exhibit standardized uptake value (SUV) errors of 20 percent or greater, particularly in areas within and adjacent to bone."

The team plans to address the issue by refining and extending novel and patented acquisition and image analysis methods it has previously developed. "By bringing together leading-edge advances in both MR acquisition and image analyses, our goal is to achieve SUVs that are within 5 percent of those obtained with PET/CT, the reference standard," Dr. Muzic says. "We will do this with clinically appropriate acquisition time, image quality and diagnostic accuracy, capable of supporting quantitative cooperative group clinical trials with commercial PET/MR systems."

For more information on MRF, contact **Vikas.Gulani@UHhospitals.org**.

For more information on PET/MR, contact **Mitchell.Machtay@UHhospitals.org, Bryan.Traughber@UHhospitals.org** or **Raymond.Muzic@case.edu**.

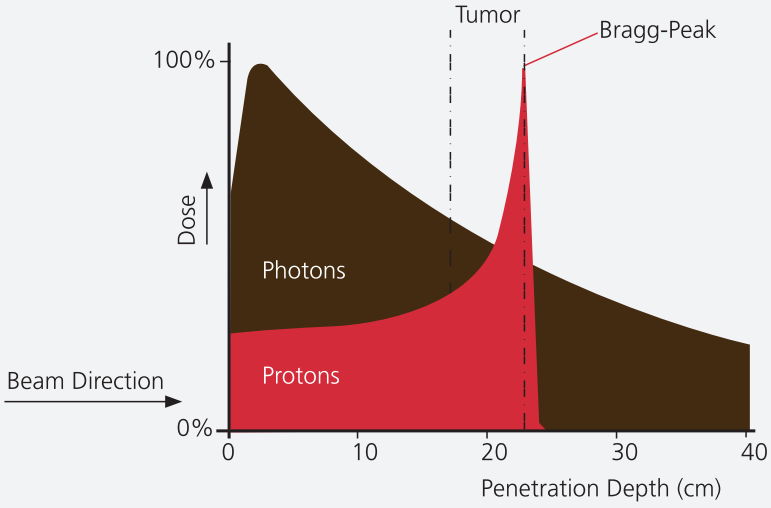
Proton Precision

New Proton Therapy Center set to debut at UH Seidman Cancer Center

Patients at University Hospitals Seidman Cancer Center will soon have access to the distinct dosimetric advantages of proton therapy, thanks to the hospital's new Proton Therapy Center, scheduled to open in summer 2016. Expected to be the first in Ohio and regionally, the Proton Therapy Center will accommodate patients from a multistate region.

While traditional proton therapy systems cost hundreds of millions of dollars to build and can be as large as a football field, the compact, gantry-mounted design of the Mevion S250 superconducting synchrocyclotron accelerator being built at UH Seidman Cancer Center requires less space, fewer staff and significantly less energy to operate, making it possible for construction to occur on the UH campus. This, in turn, grants easy access to the center by the pediatric, adolescent and young adult cancer patients at the adjacent UH Rainbow Babies & Children's Hospital – the patients likely to benefit most from proton therapy.

"Proton therapy is uniquely suited for treating pediatric and young adult population," says David Mansur, MD, Director of Pediatric and Hematologic Radiation Oncology at UH Seidman Cancer Center, who is overseeing the launch of the Proton Therapy Center. "It eliminates a lot of unnecessary low and intermediate doses, which is especially significant for pediatric patients, many of whom have curable malignancies."



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Associate Professor of Pediatrics and Radiation Oncology, Case Western Reserve University School of Medicine

An advanced form of radiation therapy, proton therapy targets tumors more directly and spares much of the surrounding tissue from the side effects of radiation. This targeted therapy can provide advantages for treatment of certain tumors, such as those in the base of the skull and in the head and neck. It is also being used in treatment of left-sided breast cancer, as the proton beam reduces radiation to the heart, potentially reducing the risk of heart disease in the years following treatment.

With greater power and precision, however, comes an enhanced focus on patient selection and risk management. "Proton therapy is a more unforgiving treatment, says Dr. Mansur. "With proton therapy, changes in density and tumor motion have a greater potential to introduce uncertainty in the radiation dose than in photon beam cases. We will be exercising caution in proper selection of patients who will benefit the most."

For patients, the differences between traditional radiation therapy and proton therapy are largely invisible. Proton therapy may minimize typical radiation therapy side effects, but patients typically have the same number of treatments.

Participation in clinical trials is expected to be an important component of care for patients treated with proton therapy at UH Seidman Cancer Center. A registry will track outcomes, and the vast majority of patients will be enrolled in a clinical trial.

Dr. Mansur says he's looking forward to the enhanced treatment options the Proton Therapy Center will offer his pediatric patients, as well as the convenient way they'll be able to access this innovative care.

"UH Seidman Cancer Center's Proton Therapy Center will be located on the same campus as a nationally ranked children's hospital," he says. "It's one of the only places in the country to achieve that distinction."

For more information about our new Proton Therapy Center, contact **David.Mansur@UHhospitals.org.**

JULIAN KIM, MD
Chief Medical Officer and Charles A. Hubay Chair in Surgery, UH Seidman Cancer Center
Professor of Surgery, Case Western Reserve University School of Medicine

Mounting an Immune Response Against Melanoma

Adoptive immunotherapy with *ex vivo*-activated T cells has shown promise among patients with malignant melanoma, including select patients with bulky, metastatic disease. However, the clinical reach of this therapy has been limited by logistical constraints on generating sufficient numbers of antigen-specific cells in a short time period.

"The process to generate activated T cells is extremely cumbersome," says Julian Kim, MD, MS, Chief Medical Officer at University Hospitals Seidman Cancer Center. "The current process takes eight weeks and relies on highly skilled people to test the cells while they're being grown in the lab. It's just not practical."

At UH Seidman Cancer Center, Dr. Kim and colleagues from the Case Comprehensive Cancer Center and National Center for Regenerative Medicine at Case Western Reserve University have discovered a way around this problem. They've developed an alternative, simplified method of generating and processing a large number of T cells for infusion. The unique, patented process shortens the time required to culture activated T cells from eight weeks to 14 to 16 days.

"There is no one else in the world who is using the process that we're using," Dr. Kim says. "It's a big collaborative effort here."

In preclinical research with T cells derived from human lymph nodes draining a melanoma tumor (melanoma-draining lymph nodes, or MDLN), Dr. Kim and his team have developed a process of T cell expansion and activation that results in melanoma-specific anti-tumor responses, both in laboratory tests and in a mouse xenograft model.

"We have evidence for the first time that the MDLN T cells contain melanoma antigen-specific CD4 and CD8 T cell populations capable of mediating *in vitro* and *in vivo* immune responses against human melanoma," Dr. Kim says.

"The activated MDLN cells demonstrated reactivity in response to overlapping peptides spanning the sequence of four different known melanoma antigens." Dr. Kim and colleagues published their findings recently in the Journal of Immunotherapy.

Buoyed by this early success, Dr. Kim and his team have launched a Phase I clinical trial, administering infusions of the activated T cells to patients with advanced melanoma. The team is monitoring patients for any significant side effects, as well as comparing different dosing regimens and using DNA sequencing to measure how long the activated T cells persist in the body.

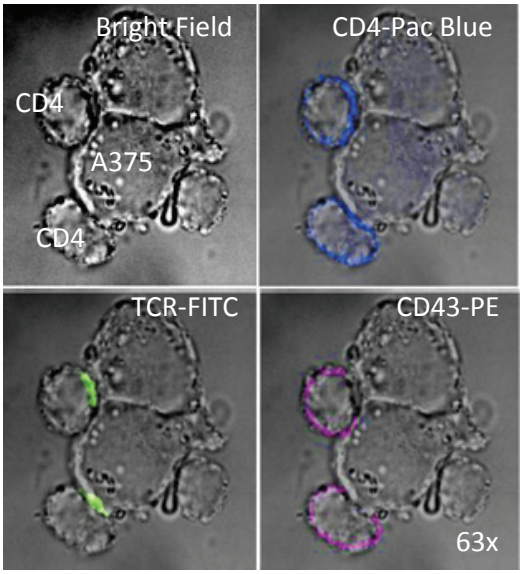
"No one really knows how many T cells patients should receive," Dr. Kim says. "All the trials in the past, they've just grown as many cells as possible and given them all to the patient. But there's some indication that when you do that, your body's immune system will actually 'push back' and develop a regulatory mechanism to suppress them."

To hone in on the optimal dose and schedule, the team is comparing immune responses among four groups of advanced melanoma patients. The first group is receiving a single dose of activated T cells, another is receiving the same dose in two infusions four weeks apart, another is receiving a double dose in two infusions four weeks apart, and the last is receiving the same double dose but administered over four infusions, four weeks apart.

"We're going to look at persistence of the infused cells and the regulatory response by the patient's immune system to determine the best dose and schedule moving forward," Dr. Kim says. "But the whole endeavor is very exciting. It's a home-grown, living therapy."

For more information on this clinical trial, contact **Julian.Kim@UHhospitals.org.**

Activated T cells cultured in shorter, patented process focus of new Phase I clinical trial at UH Seidman Cancer Center



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HYDROGEL SPACER REDUCES RECTAL RADIATION IN PROSTATE CANCER PATIENTS

UH Seidman Cancer Center radiation oncologist first in U.S. to use newly approved device

An injectable gel that expands the space between the prostate and rectum decreases rectal radiation among men undergoing radiation therapy for prostate cancer, according to new research. The study – the first prospective, randomized pivotal trial of a prostate-rectum spacer – was published recently in the International Journal of Radiation Oncology•Biology•Physics (Red Journal), the official journal of the American Society for Therapeutic Radiology and Oncology (ASTRO).

"This new hydrogel represents a significant development in advancing the safety, precision and flexibility with which prostate cancer radiotherapy can be delivered," says Rodney Ellis, MD, a radiation oncologist at University Hospitals Seidman Cancer Center and co-author of the new study.

The gel, marketed as the SpaceOAR System by Augmenix, Inc., received approval from the U.S. Food and Drug Administration in April 2015. Dr. Ellis was the first physician in the U.S. to use SpaceOAR post-approval.

The new ASTRO study involved 222 men with stage T1 or T2 prostate cancer undergoing image-guided, intensity-modulated radiation therapy. Investigators assessed spacer safety and its impact on patients' rectal irradiation, toxicity and quality of life over 15 months.

Results show that the hydrogel spacer, on average, increased prostate-rectum space from 1.6mm to 12.6mm. This extra space reduced the average rectal V70 radiation dose from 12.4 percent to 3.3 percent, a 73 percent relative reduction, when compared with those not receiving the gel. This decreased radiation led to additional benefits among the treatment group, including 76 percent fewer reports of rectal pain, 71 percent less rectal toxicity in the year following radiotherapy and 46 percent fewer reports of significant bowel problems in the year after radiotherapy.

For Dr. Ellis, this new spacer technology presents many benefit for the patients he treats, including increased opportunities for hypofractionation and dose escalation.

"Shielding the rectum from radiation allows us to increase the radiation dose used to kill cancerous cells in the prostate," he says.

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University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are consistently recognized as two of the premiere institutions in the nation, according to U.S. News & World Report.

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