Yale Cancer Center

centerpoint

MAGAZINE

Training the Next Generation of Oncologists

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Jill Lacy, MD, Director of the Medical Oncology/Hematology Fellowship Program at Yale Cancer Center with, (l-r), Mehmet Altan, MD, Yue Zhang, MD, MPH, and Nataliya Uboha, MD.

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director's letter


PETER BAKER

I AM PLEASED to share that Yale Cancer Center's designation as a Comprehensive Cancer Center by the National Cancer Institute (NCI) was recently extended for an additional 5 years following an extensive grant submission and review process. Our renewal is a reflection of the groundbreaking research efforts in our laboratories and the increasingly fast pace of translating our research findings to improved patient care and treatment options for our patients.

The NCI award includes $12.2 million in funding to support the Center's 7 research programs and 8 shared resources, along with the continuation of the Center's comprehensive status, the most prestigious level of designation from the NCI. Yale Cancer Center is one of 41 Comprehensive Cancer Centers in the nation and the only one in Connecticut. Yale was one of the first 11 cancer centers to be designated comprehensive under the National Cancer Centers plan in 1974.

I am also excited to announce the launch of the new "Yale Tobacco Center of Regulatory Science" through a $20 million grant from the U.S. Food and Drug Administration and the National Institutes of Health. The new Center will investigate the science of tobacco addiction, one of the leading risk factors for cancer, and will study how flavors, including menthol, and sweeteners affect the development of addiction to tobacco products. Researchers will also train a new generation of scientists, and provide pilot funding to stimulate research related to tobacco regulatory science. The researchers include experts in sensory perception, brain reward pathways, adolescent tobacco use, and human behavioral pharmacology, as well as health economics and decision-making.

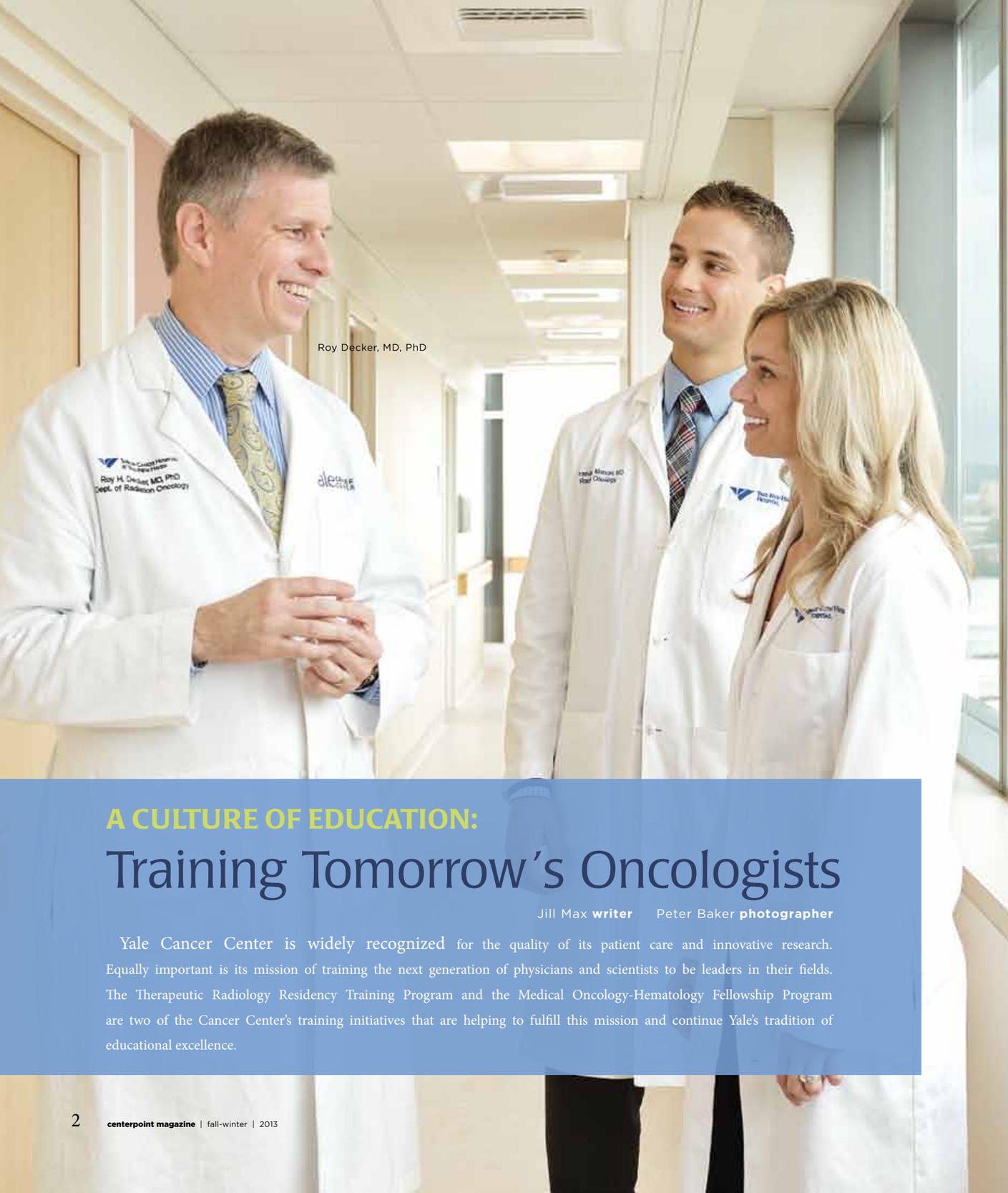
The leadership of Yale Cancer Center and Smilow Cancer Hospital at Yale New-Haven continue to focus on translational research and personalized cancer medicine. Our newest initiative toward that goal is the launch of a weekly Precision Medicine Tumor Board, led by leaders in developmental therapeutics, genetics, phase I research, and our 12 clinical program directors. Each Tumor Board reviews selected patient cases and their tumor profiles to discuss the best treatment options for the clinical team's consideration. This 'meeting of the minds' has already led to new options for patients and more opportunities for clinical trial participation.

I look forward to updating you on new research initiatives and translational research developments in the next issue of Centerpoint Magazine. Enjoy the holiday season with your families!

Sincerely,

Tom Lynch

Thomas J. Lynch, Jr., MD
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital



Roy Decker, MD, PhD

A CULTURE OF EDUCATION:

Training Tomorrow's Oncologists

Jill Max **writer** Peter Baker **photographer**

Yale Cancer Center is widely recognized for the quality of its patient care and innovative research. Equally important is its mission of training the next generation of physicians and scientists to be leaders in their fields. The Therapeutic Radiology Residency Training Program and the Medical Oncology-Hematology Fellowship Program are two of the Cancer Center's training initiatives that are helping to fulfill this mission and continue Yale's tradition of educational excellence.

One of the oldest and largest programs of its kind in the country – there will be 14 residents as of July 2014 – the Therapeutic Radiology residency program has experienced tremendous growth over the last few years. The key difference that sets it apart from other programs is its culture, according to Lynn Wilson, MD, MPH, Professor of Therapeutic Radiology, who served as director of the program from 2004 to 2013. In many programs, residents are bogged down by menial tasks, but Dr. Wilson sought to change that, an evolution that began before he took over and took years to accomplish. "As far as I'm concerned, if whatever they're involved in doesn't have some level of educational basis associated with it, they shouldn't be doing it," he said. Along with that, there is an atmosphere of collegiality and horizontal management that residents appreciate. "It's very easy to approach an attending to talk about a research opportunity or get advice on mentorship," said Kimberly Johung, MD, who completed her residency in June before joining the faculty. "You don't feel a divide that you hear of or get a sense about in other programs."

Roy Decker, MD, PhD, Associate Professor of Therapeutic Radiology, recently took over as program director and has added a new clinical education program that uses a mix of didactic lectures, case based review, and treatment planning sessions. So far the response from the residents has been enthusiastic. "Hearing it and then being asked to apply it in a more direct fashion has been a real eye opener for them," he said.

Yale's program offers unique clinical and research training opportunities. A collaboration with the Robert Wood Johnson (RWJ) Clinical Scholars Program allows trainees interested in clinical investigation to spend six months participating in RWJ coursework followed by six months spent working on two research projects. Dr. Decker, an alumnus of the program, started a Stereotactic Body Radiation Therapy Program about four years ago that has seen explosive growth and offers exciting training and educational opportunities for residents. Yale also participates in the American Board of Radiology Holman Pathway, which allows gifted residents to spend up to 21 months of time outside the clinic pursuing research.

The emphasis on research is apparent in both the Therapeutic Radiology Residency Training Program where all residents are given up to one year to pursue research, and the Medical Oncology/Hematology Fellowship Program, where half of the three-year program is devoted to clinical, translational, or basic science research that involves a hypothesis-driven approach.

Above and beyond the rich research and clinical environment, the fellowship program places a large emphasis on education. "Trying to efficiently educate them in basic science, how it translates into the clinic, and the fundamental clinical principles of oncologic and hematologic care is really a challenge," said Jill Lacy, MD, Associate Professor of Medicine (Medical Oncology) and the program's director, adding that the pace of change in hematology and oncology has been dizzying. Most of the clinical teaching is case based, with many clinical conferences each week.

The fellowship program is focused on mentoring, with each fellow overseen by a committee that tracks his or her progress, helps the fellow understand the expectations and milestones of the program, and offers career advice. Mentors aren't the only source of guidance, however. "Faculty welcome questions from fellows," said Nataliya Uboha, MD, PhD, a fellow in the program. "You always know you can get your question answered within minutes."

Both programs must adhere to rigorous requirements set forth by the Accreditation Council for Graduate Medical Education (ACGME) and both are intensely competitive, an indication of their stellar reputations: The residency program typically receives as many as 250 applications for three positions, while the fellowship program usually has over 300 applicants for eight spots. Last year, three fellows received highly sought after Young Investigator Awards from the American Society of Clinical Oncology and the American Society of Hematology. "Having three of our fellows recognized for their research efforts on a national level was an honor for our program and reflects the strong commitment of our fellows to research," said Dr. Lacy.

Mapping the Genetic Landscape of Brain Tumors

Steve Kemper **writer** Peter Baker **photographer**

Dr. Murat Günel

Meningiomas are the most common brain tumor, striking 170,000 Americans every year. Until recently they have largely been mysteries to medicine. Part of that mystery was solved earlier this year by a team of researchers led by Dr. Murat Günel, Professor of Neurosurgery, Neurobiology, and Genetics. Their discoveries promise to alter clinical treatment of patients afflicted with these tumors. The research was funded by a generous grant from the Gregory M. Kiez and Mehmet Kutman Foundation, which allowed the formation of the Brain Tumor research program at Yale.

Unlike more familiar brain tumors such as glioblastomas and medulloblastomas, which are ferociously malignant, fast growing, and usually fatal, meningiomas grow slowly and are benign 80 percent of the time. Nevertheless they can invade or pressure critical parts of the brain, causing neurological damage or stroke. They are typically treated through the invasive options of surgery or radiation. "There have been no chemotherapy options," Dr. Günel said, "because the genetic make-up of meningiomas has not been understood. Before our work, we largely did not know how these tumors happened."

Previous research had linked about half of meningiomas to a mutation of the gene NF2, though the mechanism remained unclear, as did the cause of all other meningiomas. To remedy this, Dr. Günel and his team took advantage of what he calls "the revolution of genomic technologies," carrying the cutting-edge research methods to the care of his patients after surgery. For a brain surgeon, he said, the most frustrating aspect is not to be able to cure a patient of their disease after a successful surgery. To gain a better insight into the genetic make-up of brain tumors in an attempt to achieve cure, his team, starting with Victoria Clark, a Yale MD/PhD student, genotyped and exome sequenced 300 meningioma tumors.

"We found that mutations of five genes explain around 85 percent of all benign meningiomas," Dr. Günel said. The roles played by four of the genes—AKT1, SMO, KLF4, and TRAF7 (the fifth is NF2)—were previously unknown. Further, the researchers learned that the tumors generated by these mutated genes grow in different parts of the brain. Tumors associated with NF2, for instance, tend to form in the cerebral hemispheres, whereas tumors associated with the other four genes group in areas along the front skull base.

"Thus, for the first time," wrote the team in *Science* (January 24), where the findings were announced, "it seems that the simple evaluation of a patient's MRI can offer insight into the molecular profile of the meningioma."

This genetic mapping and the resultant diagnostic insights will open the way for individualized treatments that target each type of meningioma. For instance, SMO mutations have been found in basal cell skin carcinoma and brain medulloblastomas. "There is already an FDA-approved drug for basal cell carcinoma," Dr. Günel said, "so we are testing it in the lab using cell cultures to see if the same drug has an effect on SMO mutant meningiomas." If so, he expects to begin clinical trials on patients with these tumors early in 2014.

That's good news, but SMO mutations account for less than five percent of meningiomas. NF2 mutations, on the other hand, are implicated in half of meningiomas but are not yet targeted by an FDA-approved drug. That's especially troubling since NF2 meningiomas are also the most likely to become malignant.

"But there are certain clear targets downstream of NF2 that are activated when NF2 is lost," Dr. Günel explained. "In our lab we are now testing experimental medications aimed at those." They hope to finish the testing on cell cultures within a year and then move to clinical trials. Meanwhile researchers at other institutions are in the midst of phase-II trials for a drug aimed at NF2 tumors in other types of cancer. Dr. Günel's team will incorporate those results into their studies. "There's a tidal wave of cancer research that is raising all of us," he said. "We're all learning from each other in the different cancer disciplines."

"There's a tidal wave of cancer research that is raising all of us. We're all learning from each other in the different cancer disciplines."

Dr. Murat Günel and Victoria Clark

The Yale researchers found a TRAF7 mutation in about a quarter of the meningiomas. Almost nothing is known about this gene, but wherever the team found its mutated form, they also found a better-known partner—either KLF4, a transcription factor, or AKT1, which activates the PI3K pathway. The PI3K pathway is well-known and has been implicated in cancer; several medications against it are now in clinical trials. Since TRAF7 is unstudied, Dr. Günel and his team are hoping to track its mutation through its co-existence with AKT1 and the PI3K pathway.

"It's interesting that they co-mutate," he said. "So what we are testing is, can a PI3K inhibitor affect that TRAF7 tumor? If the inhibitor breaks one leg of the cancer, can the cancer still run or does it stop?" If the PI3K inhibitor brakes the TRAF7 meningioma, the next step will be to figure out the downstream signaling mechanism of TRAF7. Because all this is unknown territory, Dr. Günel expects that exploring this gene will require more time than the other mutations associated with meningiomas.

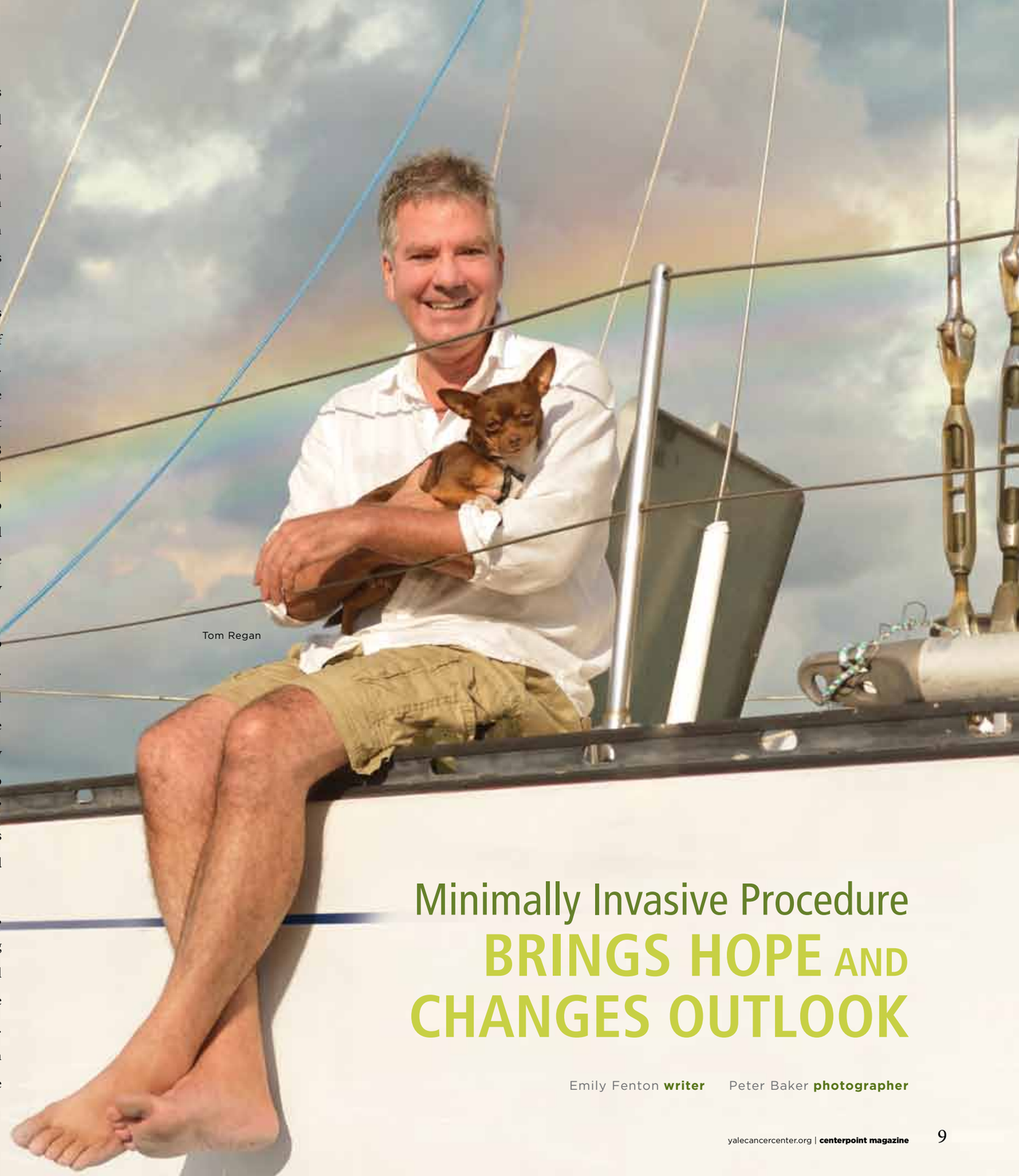
Still, Dr. Günel's team has described the genetic landscape for 85 percent of these tumors. Drugs that target each specific mutation are on the way and will soon give people with meningiomas the option of personalized chemotherapy, which will be more effective and also less invasive than the current options of surgery and radiation. In fact, Dr. Günel and his colleagues at Yale Cancer Center now have a weekly Precision Medicine Tumor Board, in which they discuss the use of targeted therapies based on the individual genomic make-up of various cancers.

The genetic mapping of benign meningiomas was relatively easy to solve, noted Dr. Günel, because they have far fewer genetic abnormalities than cancerous tumors. "But the good thing," he adds, "is that it turns out there are not infinite ways that nature creates cancer. There are only a limited number of genes involved." The new genomic technologies are tracking these down, followed quickly by new drugs that target them.

For a brain surgeon, the biggest target is the most deadly brain cancer, glioblastoma multiforme (GBM). Dr. Günel is optimistic. "We have some really exciting findings," he said. "Next time, I hope we can talk about curing some of the GBMs."

Minimally Invasive Procedure BRINGS HOPE AND CHANGES OUTLOOK

Emily Fenton **writer** Peter Baker **photographer**



Tom Regan

When Tom Regan learned that he had prostate cancer, it brought back memories of his father, who 20 years before had lost his life to the disease. Tom assumed that he was destined for the same fate. After seeking the advice of family and friends, he decided to put his care in the hands of Peter Schulam, MD, PhD, Chairman and Professor of Urology and Director of the Prostate and Urologic Cancers Program at Smilow Cancer Hospital. As a result, hope returned and his outlook began to change.

Due to the recent controversy surrounding PSA testing, Tom's primary care physician gave him the option of not having his PSA tested as part of his routine physical. Afraid of receiving bad news, Tom declined a PSA test, a decision he came to regret. Several years later, a new primary care doctor did not give him the same option, and a routine blood test revealed his PSA was elevated. He was sent to Smilow Cancer Hospital where more tests and a biopsy confirmed that Tom had high-grade prostate cancer, meaning it was likely to grow and spread, but was localized to the prostate. Tom described the next few days as a fog of tests, meetings with doctors, and scheduling of appointments, which included a second opinion at Dana-Farber Cancer Institute.

Getting a second opinion was important for Tom, and it reassured him that he was doing the right thing, but it was the first meeting with Dr. Schulam, combined with his experience and expertise, that drew Tom back to Smilow for his surgery. He met with Dr. Schulam numerous times to discuss what to expect. "Dr. Schulam was amazing and answered all of my questions, some I didn't even know I had," Tom explained. "He insisted on meeting with my wife to reassure her and answer all her questions as well. This greatly reduced the level of stress and anxiety at home." With his surgery scheduled, and treatment plan in place, Tom began what was the most difficult part for him, the waiting.

Prior to his surgery Tom had heard of the daVinci Robot and knew what to expect, but was still apprehensive about its potential adverse effects. A month after his robotic radical prostatectomy, where Dr. Schulam removed his cancerous prostate gland, Tom had for the most part resumed normal activities. "It was such a different experience than what my father went through 20 years ago," Tom explained. "He was in a lot of pain and his recovery was slow, it was tough seeing him like that. It is remarkable that now they are able to perform such a high level of surgery with such minimal side effects and pain."

Although his recovery was quick physically, mentally it was a struggle. Fifty-five years old and newly married at the time of his diagnosis, Tom described himself as healthy and vigorous. Dealing with the after effects of surgery, including incontinence and sexual side effects, was difficult. Dr. Schulam explained that improvement in continence and potency could continue for 18 months to 2 years. "It is important for patients to understand that urinary control and sexual function can take months to return and are dependent upon age, preoperative function and the type of nerve-sparing surgery that was performed. My role is to help patients have accurate expectations for their recovery and to support and reassure them."

Tom recovered well and today he is considered to have no lasting side effects. He attributes this to the skill with which Dr. Schulam performed the surgery, and the support he received from the entire Smilow team. "The staff at Smilow became like friends to me during this experience. I feel extremely fortunate to have such a wonderful prognosis and to be able to continue to live a healthy and active life with my dignity intact," Tom said. "For anyone facing a similar diagnosis I cannot stress enough how important it is to find a doctor that you trust, and to keep in mind that things do get better."

Tom is a huge advocate of men taking charge of their care, having their PSA tested, and if faced with a diagnosis, doing their research to find someone skilled to treat them. He is still coping with his diagnosis every day. Every few months he has a blood test done, and once again finds himself waiting. Tom commented, "Despite all that I have been through, I am happy to be alive. I am cancer free, and having that knowledge has definitely been worth the wait."

PETER BAKER

Liane Philpotts, MD

Tomosynthesis: The Future of Breast Cancer Screening

Digital breast tomosynthesis, or 3-D mammography, provides a 3-D image of the breast, allowing radiologists to view the breast in detailed 1mm slices, instead of as a large single image. This is important because with routine mammography, breast tissue is compressed and overlying tissue can look like a suspicious finding, requiring the patient to come back for more testing and causing what may be unnecessary anxiety. With tomosynthesis, however, these questions can be resolved immediately. With more views of the breast the radiologist can zoom in on the area in question and determine whether or not more testing is needed. This not only results in a decreased number of patient recalls, but there is also data to indicate that tomosynthesis increases cancer detection rates.

Liane Philpotts, MD, Professor of Diagnostic Radiology and Chief of Breast Imaging for the Breast Center at Smilow Cancer Hospital at Yale-New Haven, commented, "We have seen a 20% increase in cancer detection rates over 2-D mammography. In addition to that, before tomosynthesis we were calling back more than 10% of all women, which is a huge number. One of the immediate benefits that we have seen is that this number has been reduced by 30%, which is wonderful."

Currently breast tomosynthesis is being used in combination with 2-D screening mammography, as the larger picture of the breast is still necessary. However, Dr. Philpotts explained that researchers are working on ways to extract a 2-D image out of the 3-D data, known as 2-D synthetic mammography, and when that happens, there may no longer be a need for the 2-D examination. This will lessen the concern over the small increased amount of radiation patients are exposed to when using 3-D and 2-D together.

Smilow Cancer Hospital was the first center in Connecticut to offer tomosynthesis and many major centers have yet to acquire it. The benefits of the technology were realized immediately, and patients noticed no difference. Women are in the same position, with the same compression as the 2-D mammography is performed; meanwhile the tomosynthesis arm takes a sweep of the breast.

One strong advocate for the technology was a Smilow Technologist with 35 years of experience. She has watched mammography develop from film, to digital, to now 3-D. She is also one of the many patients that have benefited from this advanced technology. She commented, "I have been diligent about getting my annual screening from the age of 35, because I have dense breast tissue. Last year I had my routine ultrasound and utilized the 3-D mammography as well, both were normal. This year I once again received an ultrasound and the 3-D mammography and a small tumor was found that wasn't visible on the 2-D image." She was diagnosed with a rare form of breast cancer, invasive tubular carcinoma, which developed between screenings. "I can't imagine what would have happened had my cancer not been detected at such an early stage," she said. As it did for her, this technology can prevent more advanced cancers from developing.

"All the literature supports the fact that women benefit from this technology. It's a game changer. "

Liane Philpotts, MD

"There has been controversy regarding screening recommendations since the U.S. Preventive Services Task Force (USPSTF) released new guidelines. But with tomosynthesis, this may change," Dr. Philpotts said. "All the literature supports the fact that women benefit from this technology. It's a game changer. This could shift the risk/benefit ratio of mammographic screening."

Screening is not the only benefit that 3-D mammography has over 2-D. It can also be used to improve diagnostic mammography as it better characterizes lesions as benign or cancerous. It also makes it easier to localize things in the breast so when it comes time for an ultrasound or biopsy, the radiologist already knows where the lesion is located and what the margins are. For the Smilow Technologist this capability was a blessing not only for her, but for her patients. She commented, "I get so excited for patients when they come in and I try to make them realize what an amazing tool this is. I am a success story and know it is due to this 3-D mammography. It gives us a fighting chance against the disease."

Dr. Philpotts commented that once you see the results and how well 3-D mammography works, there is no going back. "Mammography is a great tool, it is not terribly painful for patients, and it works well. This is just building on what we already have and making it better. This will become the gold standard for breast cancer screening and diagnosis. We have embraced it here at Smilow and more importantly, our patients have too."

PETER BAKER

Alessandro Santin, MD

Targeting a Deadly Type of Uterine Cancer

Endometrial cancer, which originates in the lining of the uterus and is the most common type of gynecological cancer, often has a good prognosis. Patients with the more frequently diagnosed type I are often cured. Type II, however, is responsible for most of the recurrences and deaths that occur in endometrial cancer. Uterine Serous Carcinoma (USC), the most aggressive kind of type II endometrial cancer, accounts for just 10 percent of endometrial tumors and is particularly deadly: in its earliest stages the survival rate can be as low as 50 percent, and for those with more advanced disease, there is no cure.

"A striking majority of these patients die too early and very quickly," said Alessandro Santin, MD, Professor of Obstetrics, Gynecology & Reproductive Sciences at Yale School of Medicine and Clinical Research Program Leader of the Gynecologic Oncology Program at Smilow Cancer Hospital. Dr. Santin has spent a decade unraveling the biology of USC in an effort to develop targeted treatments that will have an impact on this devastating disease.

Dr. Santin's interest in USC was born of frustration. Before he came to Yale in 2008, he worked at the University of Arkansas for Medical Sciences, where his practice included a significant number of African American women, who have a threefold higher incidence of USC. "I was stunned by the high number of this relatively rare tumor that I was seeing every day and I wanted to understand what was responsible for its biological aggressiveness," he said. USC is resistant to chemotherapy and quickly spreads to other parts of the body. Dr. Santin wanted to find out why this was the case with the ultimate goal of developing new targets for therapy.

He began by using gene expression profiling to identify the genes that were expressed in USC tumor cells. He found that the HER2/neu receptor, which is sometimes linked to breast and ovarian cancer, was overexpressed in USC, but not in less aggressive types of endometrial cancer. He also found that patients with tumors that expressed HER2/neu had the poorest prognosis.

The drug trastuzumab (herceptin) is used to treat breast cancers that overexpress HER2/neu and was also approved last year to treat gastric cancer. Dr. Santin and his colleagues at Yale and more than a dozen institutions across the country are now using it in combination with two other chemotherapeutic agents in the first ever clinical trial to test whether it may be an effective therapy against USC.

A few years ago, Dr. Santin began to look even more deeply at the molecular pathways of USC. In collaboration with Gilead Sciences, Inc., he worked with Richard Lifton, MD, PhD, Sterling Professor of Genetics and Professor of Medicine, Joseph Schlessinger, PhD, MSc, William H. Prusoff Professor of Pharmacology and Director of the Cancer Biology Institute, and other colleagues to sequence the whole exome – the 21,000 genes that encode for proteins – of tumors from 57 women with USC. Published in the *Proceedings of the National Academy of Sciences* (PNAS) in February, their landmark study was the first to report on a large scale the genetic landscape of USC. Besides confirming Dr. Santin's earlier discovery that HER2/neu was highly expressed in USC cells, which further supports the clinical trial currently underway, it also uncovered several pathways that represent potential new drug targets.

In one pathway, the study found that the oncogene cyclin E, which helps cells proliferate, was highly active in USC due to a mutation in a gene called FBXW7. Another large group of tumors did not have the FBXW7 mutation but had the cyclin E gene amplified, illustrating that USC cells may be addicted to cyclin E in order to grow. Dr. Santin is about to begin clinical studies using a drug to target this pathway. The study also showed that about two-thirds of USC tumors either harbored a mutation in the PIK3CA gene or had amplification of this gene. This points the way to using drugs that target this pathway in other cancers to treat USC.

Other pathways related to PIK3CA that are active in tumor cells and for which there are drugs in development were also identified in USC cells, offering additional targets that Dr. Santin is testing in clinical studies.

Dr. Santin's work revealing pathways that are potentially targetable with existing drugs is allowing him to test different agents in the lab and in animals before moving to clinical trials. "It's a unique opportunity for our USC patients because we will soon be able to translate our discoveries into novel therapeutics that will improve patient outcomes," he said. "In addition to providing superior quality of care surgically, we will also be able to follow up with personalized therapies targeting key signaling pathways highly active in this lethal type of endometrial cancer."

"It's a unique opportunity for our USC patients because we will soon be able to translate our discoveries into novel therapeutics that will improve patient outcomes."

Alessandro Santin, MD

PETER BAKER

Laurel Schwartz

A Passion for Discovery

Fueled by a fascination with science and medicine and the experience of losing her husband to cancer almost 20 years ago, Laurel Schwartz is committed to supporting cancer research. But the personal connection she has with Daniel DiMaio, MD, PhD, and his work, is the driving force behind her long term contributions to support his research in tumor virology.

Schwartz and Dr. DiMaio, Deputy Director of Yale Cancer Center and Waldemar Von Zedtwitz Professor of Genetics at the School of Medicine, met through a mutual friend more than half a dozen years ago. When she heard about his research on using viruses to understand how cells work and how to manipulate them to fight cancer, she was impressed. "For me, it's critical to be involved with the person who's doing outstanding work," she said. Although Dr. DiMaio's work is unrelated to the cancer that claimed the life of her husband, Schwartz recognized the importance of learning more about the role of viruses in cancer. According to Dr. DiMaio, viruses cause about 15 percent of all human cancers, including cervical cancer, as well as forms of head and neck cancer, liver cancer, lymphoma, and Hodgkin's disease.

Schwartz's support over the past several years has allowed Dr. DiMaio to explore avenues that would otherwise have been difficult to pursue. She has funded Dr. DiMaio's work on an unusual viral protein that affects cell behavior, isolated from a papillomavirus that causes warts in cows and is related to the human papillomaviruses, which causes cervical cancer and some head and neck cancers. He has gone on to design artificial proteins based on this viral protein that block HIV infection (which is often linked to cancer), cause cells to differentiate into red blood cells, or most recently, prevent cancer formation in model cellular systems. He is pursuing this line of inquiry by exploring additional targets for these artificial proteins, attempting to simplify them and make them smaller in the hopes of developing drugs, and trying to understand the mechanisms by which they engage the cellular machinery.

"These are very much unconventional experiments," said Dr. DiMaio. "Laurel, who's been a supporter of science for many years, appreciates the necessity for continuing to do basic discovery research. She doesn't insist that we develop a new drug or a new vaccine, but rather that we understand better how cells work and how cancer forms."

Schwartz, a member of the Yale Cancer Center Director's Advisory Board, understands the value of providing an opportunity for researchers to delve into promising questions. "It's reassuring for researchers to have support in unusual areas that could be very meaningful," she said. She notes that investigators often lack the funds to pursue unusual developments sparked by their research.

The trust Schwartz places in Dr. DiMaio and the flexibility of her support are liberating, allowing him to switch directions if he sees more promising prospects. "Dan has a very good sense of long term answers, where something is going and its possibilities," she said. In an era of shrinking federal funding for research, Schwartz's donations are especially valuable because they allow him to move quickly, avoiding the cumbersome grant application and review process associated with NIH grants. At the same time, her contributions have led to important findings that have enabled him to leverage his work to obtain larger grants from the federal government.

Schwartz's interest in cancer research extends to immunology as well. Dr. DiMaio and Akiko Iwasaki, PhD, Professor of Immunobiology, are studying how viruses can block the immune system to cause cancer, and she has supported their work that defines a new mechanism of how human papillomaviruses can block immunity.

For Schwartz, passion is the key to success. She and Dr. DiMaio share a love of opera and Schwartz supports talented young opera singers through the Opera Studio at Accademia Nazionale di Santa Cecilia in Rome. It is their mutual passion for science, however, that spurs her ongoing support of his work. "It gives me satisfaction to help someone do something extraordinary," she said.

"Our job is to help define for the patient and the family what their hope is."

"These are very much unconventional experiments. Laurel appreciates the necessity for continuing to do basic discovery research. She doesn't insist that we develop a new drug or a new vaccine, but rather that we understand better how cells work and how cancer forms."

Daniel DiMaio, MD, PhD

advances

Yale Cancer Center Carves New Path in Immunotherapy

J Clin Oncol 31, 2013.

Cancer immunotherapy is showing promise in treating patients with a variety of advanced, metastatic tumors, as evidenced by two newly unveiled studies from Yale Cancer Center. Both are Phase I clinical trials.

The first study involved an investigational antibody drug, known as MPDL3280A and manufactured by Roche Genentech, which was designed to prevent a cancer cell's overexpressed PD-L1 protein from putting the immune system to sleep. Yale oncologists reported that the efficacy of MPDL3280A was evaluated in 140 patients with locally advanced or metastatic solid tumors who had exhausted other means of therapy. Tumor shrinkage was observed in patients with non-small cell lung cancer, melanoma, kidney cancer, colorectal cancer, and gastric cancer. Overall, 29 out of 140 patients (21 percent) experienced significant tumor shrinkage, and the highest number of responses were in patients with lung cancer and melanoma

In the second Phase I study, researchers evaluated the safety and efficacy of combining immunotherapy drugs — nivolumab and ipilimumab — in treating advanced melanoma. Each drug had been known to prolong survival or produce durable tumor regressions in some patients when administered individually, but combining them produced superior clinical results, researchers reported, with rapid and deep tumor regressions in many patients. Researchers provided data for 86 patients in this Phase 1 trial. They report that responses were generally durable, even in patients whose treatment was terminated early.

Brain-Penetrating Particle Attacks Deadly Cancers

Proc Nat Acad Sci. Jul 1.

Yale scientists have developed a new approach for treating a deadly brain cancer that strikes 15,000 in the United States annually and for which there is no effective long-term therapy. The researchers have shown that the approach extends the lives of laboratory animals and are preparing to seek government approval for a human clinical trial.

The researchers developed a new, ultra-small drug delivery particle that more nimbly navigates brain tissue than do existing options. They also identified and tested an existing FDA-approved drug — a fungicide called dithiazanine iodide (DI) — and found that it can kill the most aggressive tumor-causing cells. The drug-loaded nanoparticles are administered in fluid directly to the brain through a catheter, bypassing the blood-brain barrier. The particles' tiny size — their diameter is about 70 nanometers — facilitates movement within brain tissue. They release their drug load gradually, offering sustained treatment.

In tests on laboratory rats with human brain cancers, DI-loaded nanoparticles significantly increased median survival to 280 days, researchers report. Maximum median survival time for rats treated with other therapies was 180 days, and with no treatment, survival was 147 days. Tests on pigs established that the new drug-particle combination also diffuses deep into brains of large animals.

The nanoparticles are made of polymers, or strings of repeating molecules. Their size, ability to control release, and means of application help them permeate brain tissues. The scientists believe the particles can be adapted to deliver other drugs and to treat other central nervous system diseases.

Detecting Breast Cancer: 3D Screening reduces Recall Rates

Radiology. 2013 Jul 30.

Tomosynthesis, or 3-dimensional (3-D) mammography, significantly reduced the number of patients being recalled for additional testing after receiving a mammogram, a Yale Cancer Center study has found.

Tomosynthesis creates a high-resolution, three-dimensional reconstruction of the breast, which can then be viewed as sequential slices through the breast. Tomosynthesis has been shown to increase the visibility of many lesions, and helps to distinguish potentially cancerous findings from otherwise normal breast tissue.

The Yale researchers studied more than 13,000 patients who were screened. Of these, 6,100 received tomosynthesis plus mammography, and 7,058 underwent conventional digital mammography alone. The recall rate was 8.4% for patients in the tomosynthesis group, and 12% for the mammography-alone group. The addition of tomosynthesis resulted in a 30% reduction in the overall recall rate.

Q+A

meet the physician

Peter E. Schwartz, MD

John Slade Ely Professor of Gynecology, Obstetrics & Reproductive Sciences

Vice Chair, Gynecology

The Pap smear has dramatically changed the incidence of advanced stage cervical cancer. How close are we to seeing an early detection-screening test for ovarian cancer?

Unfortunately early detection for ovarian cancer remains elusive. The measurement of CA 125 levels in blood samples, along with endovaginal ultrasounds, are the mainstay in detecting ovarian cancer but there is no evidence to show that there is significant improvement in early detection using these approaches in women at high-risk for the disease or in the population at large.

You were the first to use neoadjuvant chemotherapy for advanced ovarian cancers. What impact did that have on the field of gynecologic oncology?

While I started using this approach in 1979 for highly selective patients, American medicine has been slower to adopt the use of neoadjuvant chemotherapy for advanced ovarian cancers than our European colleagues. We are now beginning to see a significant increase in the use of this approach in the U.S., which translates typically into shorter operations, less blood loss, less extensive removal of intra-abdominal organs, shorter ICU and hospital stays, and less frequent postoperative readmission rates. Up to 60% of women in major U.S. medical centers are now being treated with neoadjuvant chemotherapy.

How have surgical options for women with gynecologic cancers changed over the last decade?

Surgical options have dramatically changed over the last decade. The biggest impact has been the use of laparoscopic robotic surgery, which provides the same surgical outcomes for patients but with very small incisions, less frequent wound infections, shorter hospitalizations, and quicker recovery times.

Laparoscopic robotic surgery is available to women in need of surgery for uterine cancer, for removal of the uterus, tubes, and ovaries. It is also being offered to women with invasive cervical cancer who require a radical hysterectomy. Laparoscopic surgery is currently being evaluated for women with ovarian cancer, to determine whether optimum upfront surgical cytoreduction is possible, or if neoadjuvant chemotherapy should be used.

You were recently given the Lifetime Achievement Award by Yale Cancer Center to celebrate your career. What advice do you give the next generation of gynecologic oncologists in residency training?

The choice of a career in gynecologic oncology has been a wonderful one for me. Gynecologic oncology is one of the very few specialties where one can provide both surgical and medical treatment for patients with cancer. It allows one to develop a special, long-term relationship with their patients and their families, and gives us the opportunity to oversee all of their cancer care. The next generation of gynecologic oncologists should continue this global approach to patient management, as it has been critical to the development of advances in our field for the treatment of women with gynecologic cancers.

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