radiation treatment can also be subsequently performed, if necessary. In the meantime, nearby nerves and organs may be preserved, along with the patient’s quality of life.

"Not everyone needs treatment, and [of those who do], not everyone needs aggressive treatment," said Associate Professor of Urology Preston C. Sprenkle, MD, a pioneering advocate and practitioner of focal therapy.

Dr. Sprenkle likens this approach to treating warts: “We’re ’burning it off,’ and it may come back. But we can treat it again.”

Also called focal ablation, focal therapy is possible in part due to recent advances in magnetic resonance imaging (MRI) that allow clinicians to pinpoint a prostate cancer’s size and location and to assess its grade.

Dr. Sprenkle regularly uses magnetic resonance (MR) guidance to perform prostate biopsies. He was among the nation’s first to do so when he arrived at Yale in 2012.

“We’ve become much more specific in our ability to predict which are high-grade lesions, which are not, and where they are,” Dr. Sprenkle explained of MRI. “MR-targeted biopsy helps about half the people who are diagnosed defer their treatment to some point in the future. Some will be able to avoid treatment altogether.”

“MRI is by far the best way to image the prostate,” noted Raj Ayyagari, MD, an interventional radiologist at Smilow Cancer Hospital with expertise in real-time MRI-guided procedures. “You can see all the structures very clearly—the prostate and the tumor that you want to treat, as well as the rectum, the bladder, and the nerves.”

That clear window makes MRI the perfect guide for focal therapy, and Dr. Sprenkle uses it to deliver cryotherapy that leaves noncancerous areas of the prostate intact.

Besides cryotherapy, which targets tissue with cold gases like argon, Dr. Sprenkle also offers a type of focal therapy called electroporation. Other ablation options use lasers, high-intensity focused ultrasound (HIFU), or photodynamic therapy, in which the prostate is sensitized with a drug, then subjected to a light beam.

Soon, Drs. Sprenkle and Ayyagari will start offering a new FDA-cleared option to treat localized prostate cancer: transurethral localized sonographic ablation (TULSA). Like other focal therapies, TULSA is minimally invasive, but offers additional benefits, including added protection of surrounding tissues.

TULSA takes place in an MRI scanner with the patient under anesthesia. A slender ultrasound probe is placed in the urethra, which lies within the prostate. Cooling probes protect the urethra and rectum from ultrasound energy. A digital targeting system then allows for precise targeted ultrasonic ablation of the prostate, its direction and temperature controlled via MRI.

Smilow Cancer Hospital will be one of just a handful of centers around the world to offer TULSA, and the only one in New England. In large international trials, TULSA was safe and well-tolerated. Three-year results found that ablation had been safe and precise, resulted in greatly lowered levels of prostate-specific antigen, and left men with stable urinary and bowel function as well as erectile function that recovered by the one-year mark. The procedure may also relieve lower urinary tract symptoms.

“TULSA is not the equivalent of surgery, by any means, but it appears to be better than any other focal therapy,” Dr. Ayyagari said. After TULSA, some men in the trials did eventually need salvage therapy, such as surgical prostatectomy.

That’s to be expected, according to Dr. Sprenkle. “Focal therapy is not as definitive as surgery—that’s our point,” he said. “We’re trying to minimize the toxicity” of prostate treatment, he added. He keeps close watch on his patients after focal therapy with periodic MRI-guided biopsies.

“We can always either do a repeat ablation or redo surgery or radiation if we need to in the future,” Dr. Sprenkle said. “We’re not really losing out on much by performing focal therapy, but we may potentially be curing these people of their disease.”
Dr. Martin leads a team of surgeons, pathologists, medical oncologists, chemists, biologists, radiologists, and machine-learning engineers. "Our department has invested in the science to help the clinical aspect," Dr. Martin said.

In 2019, Martin's team reported their discovery that a membrane protein called GPI130 is rampant in aggressive and dangerous forms of bladder cancer. This protein is involved in some tumors' resistance to chemotherapy, and inhibiting its presence makes cancer cells less prone to survive and metastasize, Dr. Martin found.

Dr. Martin developed a nanoparticle shrouded in a viscous carbohydrate called Chitosan that is derived from the shells of crustaceans. He then loaded the nanoparticle with an siRNA that targets Survivin, a protein that allows tumor cells to live too long, and with another protein that penetrates cells. The newly created nanoparticle succeeded in penetrating bladder cells, decreasing Survivin levels and with people's diverse immune systems?

"Why are some prostate cancers lethal, while so many others linger harmlessly for years? How can a drug instilled in the bladder adhere in pursuit of cancer cells rather than washing out with the urine? And how can we study the multitude of possible interactions between a cancer drug and people's diverse immune systems?" Yale Urology translational research scientist Darryl Martin, PhD, is tackling questions like these with a bench-to-bedside team intent on finding better genitourinary cancer treatments. Trained in cancer molecular biology, Dr. Martin has developed innovative tools like drug-ferrying nanoparticles and mice that carry both the tumor and the immune cells of a specific human cancer patient.

Darryl Martin, PhD

In a mouse model, the nanoparticles shrank tumors by nearly three-quarters. Eventually, researchers could build a library of such mouse models, each with a slightly differing cancer and immune-system variation that could allow for more tailored cancer treatment. As with all the Martin lab's projects, the mouse model's goal is near-term clinical relevance. Disease progression, the process by which an early-stage or indolent cancer can turn malignant, is still poorly understood. Dr. Martin is working to untangle the pathways and genes involved in this tipping-point aspect of tumor behavior.

"A key part of the explanation, he suspects, lies in how each tumor is affected by its immediate surroundings, or microenvironment. The microenvironment comprises everything from blood vessels to collagen and enzymes to immune cells. Each may influence what a tumor does next. But studying the immune system's influence on tumors is hampered by the fact that researchers rely on mice that lack an immune system."

"By encapsulating a treatment, these materials could actually stick to the wall," Dr. Martin explained. "This allows the amount of time of exposure to be extended so it doesn't wash out right away—it has a chance to stay and release a therapeutic agent over time."

So far, the Martin lab has found promising results with particles that interact with cells in superficial bladder cancers. The bigger challenge is to develop a generation of nanoparticles that can penetrate deeper layers of the bladder and target more aggressive cancers. Nanoparticles also hold promise for treating prostate cancer. When Dr. Martin studied biopsies from Smilow Cancer Hospital patients with prostate cancer, he found that a receptor called Claudin is upregulated in the higher-grade cancers.

"The dream is that we could have imaging materials and therapeutic materials in one nanoparticle," Dr. Martin explained. "It could illuminate the tumor and start releasing therapeutics to that site."

By creating a nanoparticle that targets Survivin, a protein that allows tumor cells to live too long, and with another protein that penetrates cells, the newly created nanoparticles succeeded in penetrating bladder cells, decreasing Survivin levels and inhibiting growth of the cells. "The dream is that we could have imaging materials and therapeutic materials in one nanoparticle," Dr. Martin explained. "It could illuminate the tumor and start releasing therapeutics to that site."

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To block GPI130, his team created nanoparticles laden with small interfering RNA (siRNA)—genetic molecules that can disrupt specific out-of-control gene-expression pathways. In a mouse model, the nanoparticles shrank tumors by nearly three-quarters.

These nanoparticles hold promise, too, in overcoming complications with intravesical therapy, a method in which a bladder cancer treatment agent is introduced directly into the bladder. Unfortunately, these agents tend not to adhere to the bladder wall or penetrate the surface layer of cells. Their contact with the tumor is brief, quickly washing out with the urine.

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