Woes of Bladder and Prostate Cancer

A person is diagnosed with bladder cancer. It may be superficial bladder cancer, but it won’t matter. Copious pain, bleeding, risk of infection, risk of perforating the bladder, time off from work, and expense will be the patient’s ordeal.

Every three months of the first year after diagnosis, the patient must get a cystoscopy, looking inside the bladder with a camera. When we look inside the bladder, oftentimes we see little red spots and areas that ordinarily would be of no concern. But in a patient with bladder cancer, we must be concerned with everything, because the naked eye cannot always tell whether the tumor is benign or malignant. So, the patient must get a biopsy every three months, particularly early in the disease course. This is a lifelong experience—lifelong surveillance.

Bladder cancer—more than any other cancer—is the most expensive disease to care for over the course of a lifetime. Can we find a better way to see not only inside the bladder but also beyond the lining of the bladder, inside the wall at a microscopic level, without taking a biopsy, saving the patient from so much morbidity?

We want to create a better way to look inside the walls of a bladder for cancerous cells, eliminating the constant need for biopsies and saving the patient so much morbidity.

A Burning Aspiration

I’m a urologist, and my specialty is urologic oncology. I care for patients predominantly with bladder, prostate, kidney, and testicular cancer, where I’m removing mostly bladders and prostates, and some kidneys and testes. I see a large volume of patients with these diseases.

The treatment is multifaceted, including surgical therapy, chemotherapy, and radiation therapy. Our multidisciplinary care team includes the medical oncologist, radiation oncologist, pathologist, radiologist, and urologist. At the heart of the treatment is a lot of basic science and translational research.
But until we are able to cure all of these diseases, particularly prostate and bladder cancers, at a 100 percent cure rate, we need to focus also on understanding the biology, natural history, and genetics of these diseases. This has been my burning desire—to understand these facets of the diseases with more clarity and to discover how we can apply what we learn in the lab to clinical medicine and patient care.

Seeing to Cure

About six years ago, I was at a meeting in Ithaca, where I met several biomedical engineers and applied physicists. As we began talking, I explained these same problems. How do we see microscopic findings without a biopsy? The optical biopsy has always been the Holy Grail of futuristic medicine. Can we look inside someone’s body without taking a biopsy? This is where my interest in multiphoton endoscopy (MPE) began, and we struck up a collaborative search.

How do we create something to put inside a patient and perform in vivo multiphoton imaging of living human tissue. Multiphoton microscopy (MPM) is the brainchild of Cornell professor Watt Webb, Applied and Engineering Physics. It has been utilized mostly for ex vivo imaging, like any microscopy—you take a piece of tissue out and look at it. How do we create an endoscope?

The Collaborative Search

Researchers at Ithaca and Weill Cornell are working in parallel on the problem. The engineering group in Ithaca is fabricating the actual endoscope: the optics, lenses, and lasers. At Weill Cornell, we are developing the paradigm in humans, creating an atlas of multiphoton imaging to define its extent and understand its imaging properties.

We are creating a whole new field of microscopy that allows physicians to see the same features they would see using H&E staining, but with multiphoton imaging to see if the two methods are in sync with one another. Physicians and pathologists are used to looking at H&E staining, the standard for biopsies. No one has this experience looking at multiphoton imaging.

**Fascinating!**

Multiphoton microscopy allows imaging directly through living tissue. Multiphoton endoscopy is like a multiphoton camera that can be inserted into the body to do real-time imaging, averting the need for so many biopsies.

The multiphoton endoscopy project has an interdisciplinary team of clinicians, physicists, biomedical scientists, and engineers. Watt Webb and Chris Xu, Applied and Engineering Physics, are at the center of the project. With a team in the College of Veterinary Medicine, including Alexander Nikitin in Biomedical Sciences, Warren Zipfel in Biomedical Engineering, and a group of about 15 clinicians at Weill Cornell, we have brought together a fascinating group from Weill Cornell and the Ithaca campus.

These images are from the bladder. The colorful ones are the multiphoton microscopy [MPM] images, and the purple ones next to them are the H&E images. An advantage of multiphoton imaging over H&E imaging is that we can do what is called Z-stacking. When we take a biopsy, we are taking a frozen minute in time, looking at that section.

Multiphoton imaging lets us start with the superficial and image deep without moving the scope by adjusting the laser. This is in two dimensions, but effectively we are seeing it in three dimensions where we can Z-stack the images. We have a stack of about 50 images, and we can focus in and out and actually see in real time where tumor cells are and if they are superficial or going deeper into a layer.
The Watt Webb and Chris Xu, Applied and Engineering Physics Team

Multiphoton Endoscope Prototype
It’s a tremendously exciting time to be a doctor. **Technology is exploding.** Only a few fields could allow me to put together diverse collaborations, working with so many different disciplines all trying to achieve the same goal of improving patient care. Translational research is the ultimate gratification—helping patients, improving technology, and improving science. At the same time, it allows me to be a lifelong student. Every day I feel like I’m still a student. The minute I’m no longer learning, it’s time to hang it up.
What are we seeing when viewing multiphoton images? In our blind testing, a group of pathologists examine several different organ systems—the bladder, colon, breast, thyroid, ovary, and lung. We take an excised piece of human tissue, image it using both the H&E and multiphoton methods. We then compare the two to see if we can be diagnostically as accurate using multiphoton diagnostics as we can with H&E.

**Overcoming a Major Challenge**
It’s a major challenge to compare an H&E image to a multiphoton image. First, we need to be sure that we are looking at the same exact spot of tissue. Looking under a microscope that has 40x magnification, if we are one micron off, we will be looking at totally different cell types. Sushmita Mukherjee, director of the multiphoton microscopy core facility at Weill, has been instrumental in fine-tuning the optical parameters of the multiphoton scope and has helped in the development of the multiphoton atlas.

We developed a technique called a punch biopsy of the tumor. We take a tiny needle with a hollow core and push it into the tissue to remove a tiny cylinder of tissue. This way we are only looking at that one cylinder spot. We shave a slice of the cylinder and image it. This technique ensures that we are imaging the exact spot under both H&E and multiphoton methods.

**Seeing Cancer Stage and Grade**
With cancer, we want to figure out stage and grade. Stage refers to how deep into the bladder wall the tumor invades. The bladder is made up of several layers. The first layer, mucosa, is where cancers start. The mucosa is lined with transitional cells. A cancer of the lining of the bladder is called transitional cell carcinoma. The second layer, lamina propria, consists of many small blood vessels and lymphatic vessels. Underneath is a muscle layer and on the outside is fat.

Determining stage means finding exactly where in the wall the tumor invades. About 70 percent of bladder tumors are superficial, meaning they are confined to the lining of the bladder, but the other 30 percent invade deeper into the bladder wall.

One of our major goals in multiphoton imaging is to specify stage. Can we determine depth? We discovered that this imaging can penetrate about 500 microns, which is enough to get through the mucosa and into the lamina propria layers, but not into the muscle. Diagnostically, this is invaluable.

We would be able to see if the tumor has penetrated the first layer of the bladder, and this in part will give us the stage. To find out if the cancer has gone into deeper layers, we scrape away the top part of it and reimage.

The biologic aggressiveness of the cells is the cancer’s grade. Bladder cancer can be low grade, meaning the cells look only slightly abnormal, and they do not have the propensity or the ability escape the bladder. Alternatively, they can be high grade, where the cells look bizarre—very unusual in appearance. These cells do have the ability to escape the bladder and metastasize.

**Multiphoton Endoscopy at the Proving Ground**
The standard method for diagnosing tumors and cancers is the biopsy—taking a piece of tissue and processing it. We want to do this whole process using a multiphoton microscope—the optical biopsy.

We are developing multiphoton endoscopy as a proof-of-principle concept. Once the endoscope is ready, we will have justified the MPE as a legitimate method for assessing histologic images of tissue and making diagnoses. The work at Weill Cornell and Ithaca will converge, and we can begin to look at endoscopic images.

We’re very close. We have published several papers, and the accuracy of our pathologists in diagnosing tumors using MPE is quite impressive. We are completing an animal prototype to be tested at the Cornell veterinary college. Chris Xu, Applied and Engineering Physics, and Alex Nikitin, College of Veterinary Medicine, are working closely to do the initial small animal imaging and ultimately larger animal imaging.