A PUBLICATION OF **THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND** | THE BRADY UROLOGICAL INSTITUTE | JOHNS HOPKINS MEDICINE

DISCOVERY

VOLUME 12 | WINTER 2016

Carter and Epstein: *Making active surveillance safer and the Gleason scores easier to understand.*

INSIDE THIS ISSUE:

Active Surveillance: Good News for Men with Low-Risk Prostate Cancer

The Brady's Active Surveillance program has reached a milestone: 20 years of carefully following men with low-risk prostate cancer. "What we have learned since 1995 can help many men with low-grade, low-risk prostate cancer, and their doctors, determine their best course of treatment," says urologist H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology, a pioneer in the active surveillance of prostate cancer. "There is increasing evidence that monitoring favorable-risk prostate cancer does not lead to worse outcomes when compared to immediate treatment. This is good news for the majority of men diagnosed today."

When the Active Surveillance program first started, "many urologists believed this approach was ill-advised for any man with a diagnosis of prostate cancer," Carter notes, "for fear of losing the

Continued on page 4»

What Kind of Prostate Cancer Do I Have? Epstein Develops a Less-Confusing System

After all the worry — the elevated PSA, then the biopsy — the diagnosis is finally here. You just found out that you have prostate cancer and the Gleason score is a 3+3=6. What does that even mean? You look it up; the literature your doctor provided says that "the score is the sum of the most common and second-most common Gleason patterns." Apparently, the lowest score is 2 (1+1) and the highest is 10 (5+5) — and you are a 6. That looks like you're on the more significant end of the spectrum.

It's not easy for most men to understand their prostate cancer stage right away, because the way Gleason scores are determined is just plain confusing. Epstein's new system cuts through the numbers.

Wrong. Nobody gets a Gleason 2; they aren't ever diagnosed on needle biopsies. "In fact, Gleason 6 is as good as it gets," says urologist Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. It's not easy for most men to figure this out right away, because the way Gleason scores are are determined is just plain confusing – unless you're a pathologist, seeing how a bunch of cells look under the microscope, and noticing which two combined patterns of cells are most prevalent.

Brady pathologist Jonathan Epstein, M.D., the Rose-Lee and Keith Reinhard Professor of Urologic Pathology, wants to make it easier for men to understand their prostate cancer

Continued on page 3»

A New Way to Attack Early Metastatic Disease

There are bits of cancer that have spread, or metastasized, beyond the prostate, but not that many, and not at very many locations in the body. Cancer in this state is still vulnerable, and still responds to treatment.

In the blockbuster movie, *Independence Day*, terrifying space aliens invade earth. From one mother ship, dozens of equally deadly, smaller ships spread out around the planet. But these evil aliens are beaten by a tiny home force. The secret? They attack the mother ship, and without its protection, the smaller ships are vulnerable.

This is a pretty good model for what radiation oncologist Phuoc T. Tran, M.D., Ph.D., wants to do with metastatic prostate cancer in its earliest stages. He believes that by eliminating the bigger sites of cancer, tiny new ones won't be able to flourish. It's an idea that has shown success in the treatment of breast cancer, "where improved local control decreases metastatic as well as local relapse," Tran says. "This local treatment model is true for prostate cancer, too. Better control of localized cancer by adjuvant radiation to the area around the prostate (called the prostatic bed) lowers the risk of other metastases and improves overall survival. We believe that sites of *macroscopic* disease — visible on MRI or other images — support the maturation of *microscopic* spots of cancer into future metastases." Going after the cancer that can be seen "has substantial clinical implications" for the cancer too small to be seen, he adds. "This is hardly ever performed in prostate cancer."

In the spectrum of cancer, from localized to advanced metastatic disease, is a kind of midpoint called an *oligometastatic* state. There are bits of cancer that have spread, or metastasized, beyond the prostate, but not that many, and not at very many locations in the body. Cancer in this state is still vulnerable, and still responds to treatment. For example, "in patients with oligometastatic sarcomas or colorectal cancer, local radiation to the primary tumor combinedwith chemotherapy, can result in long term disease-free survival in between 25 and 40 percent of patients," says Tran. "Our own clinical experience suggests an oligometastatic state exists in a subset of prostate cancer patients who may benefit from local radiation treatment to all sites of macroscopic metastatic disease."

Picture, if you will, the bloodstream. It goes throughout the body, flowing in one direction. Cancer cells that make their way into the blood, like seeds floating on a river, leave the original tumor — the mother ship — and drift for a while, eventually coming to rest at a distant site, where they may start to grow. This is the generally accepted model of how cancer spreads. But Tran suspects that these circulating tumor cells (CTCs) get homesick — that they pay an occasional visit back to the original tumor, or maybe visit one of their siblings that has struck out on its own and built a home. These visits are invigorating: "The CTCs become more robust," he says, "and this cyclical process of CTCs interacting with more established cancer results in the release of signals that foster tumor growth." Like a domino effect, then, tumor growth leads to angiogenesis — the paving of new roads, made of blood vessels, to supply the tumor; angiogenesis is followed by immune evasion – the cancer mutates to dodge the body's militia of immune cells — and ultimately, "the formation of new, macroscopic metastases." This theory of macroscopic metastases being self-seeding communal sanctuaries is supported by recent genomic data from studies of human prostate cancer cells, Tran says.

What's the best way to target these little blots of cancer? Tran believes the key is stereotactic ablative radiation (SABR), "a highly focused, localized, high-dose radiation delivered in a hypofractionated course," meaning in several large doses, spread out over several days. "It's ideally suited for treatment of oligometastatic patients, and has shown high local control rates with minimal toxicity," he says. "SABR effectively targets the microenvironment of tumors, and in melanoma patients, has been shown to have antitumor effects on the irradiated tumor and an abscopal effect" — think of a shock wave, affecting areas not part of the original blast — "on distant metastases when combined with other immune system-stimulating agents."

Tran is starting a multi-institutional study aimed at killing oligometastatic cancer through SABR and immune system-targeting agents. This program is partly funded by an award from the National Cancer Institute to radiation oncologist Ted DeWeese and Director of Nuclear Medicine Martin Pomper, and by a Movember-Prostate Cancer Foundation Challenge award to Tran, who is the principal investigator, and to urologist Ashley Ross, DeWeese, Pomper, Adam Dicker (from Thomas Jefferson University), Max Diehn (from Stanford University), Charles Drake, Hao Wang, Kenneth Pienta and Mario Eisenberger.

In 2015, among other honors and awards, Tran was appointed Clinical Director of Radiation Oncology and was named Associate Editor for the journal, *Cancer Research*. ■

Capturing Cancer Cells in the Bone, Years Before They Cause Trouble

Brady surgeons and scientists are working together, using a surgical technique pioneered by three of our urologists, to target potentially lethal prostate cancer before it has a chance to spread. "The key here involves what we call disseminated tumor cells, or DTCs," explains Ken Pienta, M.D., the Don Coffey Professor of Urology. "We can detect them at the time of radical prostatectomy — these tiny prostate cancer cells that have escaped the prostate and taken up residence in the bone marrow."

Important note: DTCs are not the same thing as bone metastases. Just because a man has these cancer cells in his bone marrow doesn't mean that he has cancer growing in his bone, Pienta hastens to point out. The purpose of this story is not to scare anybody, but to tell you about exciting work that has the potential to allow doctors to see into the future, through a microscope, and identify trouble-making cells years before they are able to cause a problem.

At the moment, Pienta and colleagues don't know exactly what to make of these DTCs. "They remain poorly defined," he says, "but we think they are a mixture of passively sloughed, nonlethal cells that are going to die anyway — which means they're nothing to worry about — but in some cases they could also be actively migrating, cancer cells that could eventually develop into clinical metastases. It is very important to study these DTCs so we can determine how to stop the lethal ones. Previously, it was reported that nearly all men have these cancer cells in their bone marrow at the time of surgery. Now we have the know-how to prove how many men have these cancer cells in their bones, so we can go after that cancer."

In laboratory research, Brady resident Michael Gorin has developed sensitive new methods to detect and capture these cells for analysis, Pienta says. And three Brady surgeons — Ashley Ross, Ted Schaeffer, and Alan Partin — have pioneered a painless technique to sample the marrow from the pubic bone just before radical prostatectomy, when the patient is asleep. "This has never been done before and represents an exciting new advance for the field," says Pienta. "The team has already obtained samples from more than 50 men and we are busy characterizing these cells. We expect to study 500 men in the coming year; this will be the largest study ever performed to characterize DTCs in men at the time of surgery."

Pienta and colleagues believe this research will identify the early steps by which lethal prostate cancer "develops and metastasizes to the bone marrow microenvironment, opening the door for early therapeutic intervention to decrease deaths from prostate cancer." ■

***Long days, short weekends, unparalleled research experience**: Mentor Sarah Amend, a postdoctoral fellow in Kenneth Pienta's lab, with student Sounak Roy.*

Summer Urological Research Experience (SURE)

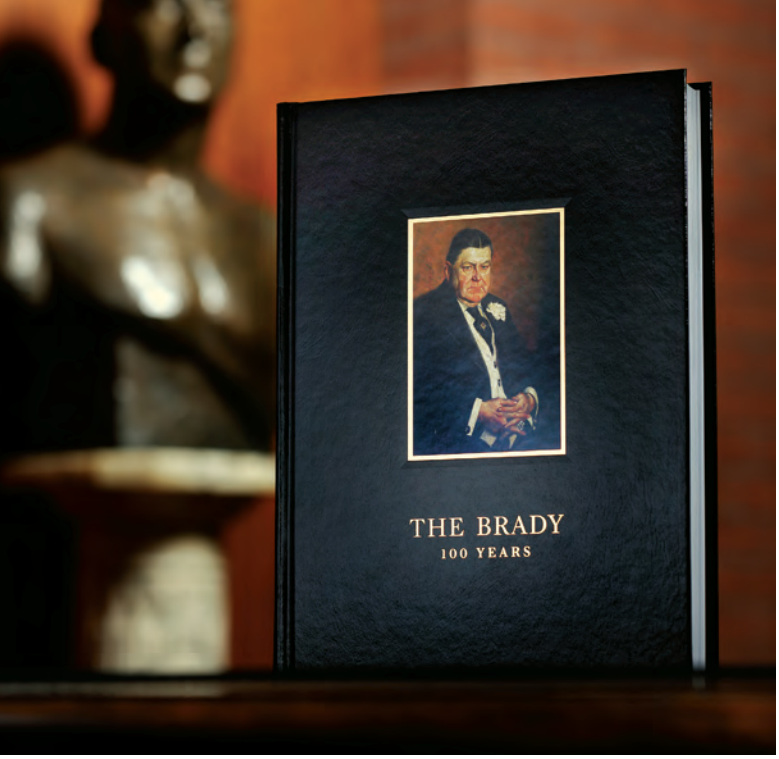
It may not be a particularly restful summer vacation, but it "SURE" is a one-of-a-kind chance for students who are interested in urological and cancer research to learn from some of top scientists in the field, in the laboratory and at lectures and seminars. "It's a wonderful opportunity for young investigators to see how research done at the bench can be translated into patient care," says Ken Pienta, M.D., the Donald S. Coffey Professor of Urology and Director of Research. The 10-week program offers a stipend of $3,000. Housing is provided near the Johns Hopkins University, and shuttle transportation to the medical campus is free.

"This summer internship requires a full-time commitment," says Pienta. "Interns should be prepared for long days and short weekends. But the experience is unparalleled."

If you would like to support this wonderful program or even sponsor a student, please see the envelope in this issue of Discovery.

Want to learn more? To find earlier issues of *Discovery* – and much more – check out our website: urology.jhu.edu

If you do not wish to receive this newsletter, please write to us at The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore MD 21287-2101.



"A triumph of storytelling and design."

—**Keith Reinhard,** *Chairman Emeritus, DDB Worldwide*

Download the e-book FREE at:
urology.jhu.edu/about/history/Brady100years

Currently available to the public in e-book format only, abridged Kindle edition coming soon.

THE BRADY: 100 YEARS

A History of the James Buchanan Brady Urological Institute at Johns Hopkins

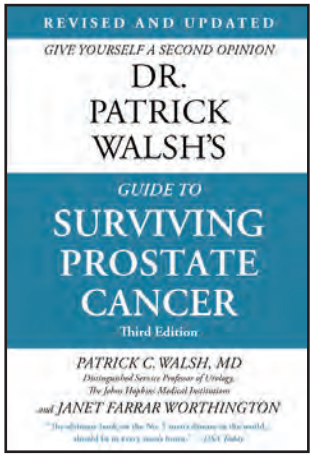
By Patrick C. Walsh and Janet Farrar Worthington
Featuring 380 Richly Illustrated Pages

For a century, the Brady has been the world's leading urological institute. Read about our past, meet our scientists and faculty members, and join us as we look ahead to the next 100 years! In this richly illustrated book, packed with stories that bring some of the greatest names in Urology to life, you'll learn:

- How James "Diamond Jim" Brady was cured of BPH and donated the money to start this institution.
- How Hugh Hampton Young, a brilliant innovator who designed and built many of his own surgical devices, became the Father of Modern Urology, transforming the field into a major surgical specialty.
- How William Scott transformed the urology residency, allowing the Brady to produce some of the world's best surgeon-scientists.
- How Patrick Walsh revolutionized the surgical treatment of prostate cancer, changing the field of prostate cancer treatment and research forever.
- How Alan Partin continues the Brady's tradition of excellence today, as we look forward to our next 100 years!

The Bestselling Book on Prostate Cancer

Comprehensive, reassuring and full of hope. Now available as an eBook and on Kindle!



COMPLETELY UPDATED 3RD EDITION

With this book you will learn answers to these and other important questions:

- Why do I need to have a baseline PSA at age 40? I thought it was age 50!
- If there is no magic PSA cutoff point, how can my cancer be diagnosed?
- What is the most up-to-date information on surgery and radiation therapy?
- Have there been any breakthrough tratments in the management of advanced disease?

Available from Warner Wellness: www.hgbusa.com or call 800.759.0190

Discovery is published by

THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE

Johns Hopkins Medical Institutions
Baltimore, Maryland 21287-2101
410.955.8434 | urology.jhu.edu

Patrick Walsh, M.D., *University Distinguished Service Professor of Urology*
Janet Farrar Worthington *Writer/Editor*
Hatcher Design Office *Art Direction*
Kieth Weller *Principal Photography*