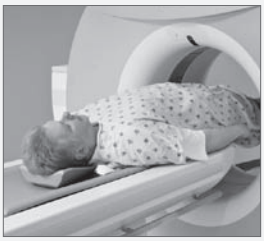
HARVARD MEDICAL SCHOOL

2011 *Annual Report on* PROSTATE DISEASES

Covering advances in the diagnosis and treatment of prostate cancer, BPH, erectile dysfunction, prostatitis, and related conditions



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2011 *Annual Report on Prostate Diseases*

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Marc B. Garnick, M.D., Editor in Chief

Dr. Garnick is an internationally renowned expert in medical oncology and urologic cancer. A clinical professor of medicine at Harvard Medical School, he also maintains an active clinical practice at Beth Israel Deaconess Medical Center, and has dedicated his career to the development of new therapies for prostate cancer. The *Annual Report on Prostate Diseases,* formerly *Perspectives on Prostate Disease,* emerged from Dr. Garnick's keen interest in explaining issues of medical importance to patients and their families in order to help them select appropriate treatments. He has authored numerous scientific articles and reviews on clinical research, drug development, and cancer biology and has written or edited six books, including *A Patient's Guide to Prostate Cancer.* In addition to his academic affiliations, Dr. Garnick founded the Hershey Family Foundation for Prostate Cancer Research at Beth Israel Deaconess Medical Center, serves as medical advisor to *World Book Encyclopedia,* and serves on the boards of trustees of Bowdoin College and the University of Pennsylvania School of Medicine and Penn Medicine.

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David S. Rosenthal, M.D., a past President of the American Cancer Society, is currently a Professor of Medicine at Harvard Medical School and Director and Chief Executive Officer of Harvard University Health Service, coordinating the care and management of 35,000 members of the Harvard University community. Dr. Rosenthal is also the Medical Director of the Leonard P. Zakim Center for Integrative Therapies at Dana-Farber Cancer Institute, which seeks to integrate complementary therapies with conventional cancer treatments. He is the author of numerous scientific articles as well as several publications for laypeople, including *The American Cancer Society's Guide to Complementary and Alternative Cancer Methods.*

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Cora N. Sternberg, M.D., F.A.C.P., is an internationally respected leader in medical oncology and urologic cancer. She is Chief of the Department of Medical Oncology at the San Camillo–Forlanini Hospital and an Adjunct Professor at La Sapienza University, both in Rome. The scientific coordinator of many international conferences, Dr. Sternberg is an elected board member of the European Organization for Research and Treatment of Cancer and serves as Coordinator for Genitourinary Oncology Education for the European Society for Medical Oncology. She has authored numerous scientific articles and co-edited three textbooks, and she serves on the editorial boards of several international journals.

Anthony L. Zietman, M.D., is a Professor of Radiation Oncology at Harvard Medical School and a radiation oncologist at Massachusetts General Hospital. In addition, he is President of the American Society for Radiation Oncology, serves on the genitourinary committee of the Radiation Therapy Oncology Group, and is a Trustee of the American Board of Radiology. Dr. Zietman's research interests include the role of active surveillance, brachytherapy, hormone therapy, and proton beam therapy in the treatment of prostate cancer. He has authored more than 100 articles and reviews on many aspects of genitourinary cancer.

PHYSICIAN INTERVIEW

Targeted focal therapy for early-stage prostate cancer

Minimally invasive technique may effectively control cancer without compromising quality of life

When it comes to treating early-stage prostate cancer, options abound. At one end of the spectrum, patients can choose between doing nothing and active surveillance (postponing treatment of the cancer until it shows signs of progression with regularly scheduled follow-up tests). However, many physicians, including renowned urology researcher E. David Crawford, M.D., aren't comfortable suggesting these strategies to patients, especially those men who are likely to live more than 15 years. Crawford provocatively likens active surveillance to Russian roulette because by the time patients undergo treatment, the cancer may have advanced to the point where it can no longer be eradicated.

But treatments at the other end of the spectrum, including radical prostatectomy and radiation therapy, aren't ideal either. With these options, a man with a tiny tumor in just one part of his prostate risks urinary incontinence, impotence, and other complications that could dramatically affect his quality of life and, as recent studies suggest, does little to prolong his life. This, says Crawford, is the equivalent of treating cancer with an ax, but when told that they have cancer, most patients want it taken out right away.

Targeted focal therapy,* which uses minimally invasive techniques, could be a viable, middle-of-the-road solution. Treatment could focus specifically on the tumor, rather than the entire prostate. In theory, this would prevent the cancer from growing out of control while minimizing life-altering complications.

As chairman of the Southwest Oncology Group (SWOG) Genitourinary Committee for 28 years and senior associate director of the Comprehensive Cancer Center at the University of Colorado Health Sciences Center in Denver, Crawford has done many clinical trials, including studies that test targeted focal therapies. (A network of medical centers, universities, oncologists, scientists, statisticians, and administrators, SWOG develops and runs clinical trials.) Crawford, who is also a professor of surgery, urology, and radiation oncology, spoke with the editors of the *2011 Annual Report on Prostate Diseases* about his research and the potential of targeted therapy for prostate cancer treatment in appropriately selected patients.

What is targeted therapy?

Instead of removing or ablating the whole prostate, targeted therapy, also called focal therapy, treats the part of the prostate where the cancer is located. You can compare focal therapy to a lumpectomy done for breast cancer; instead of mastectomy, which involves the removal of the entire breast, a lumpectomy means that only the cancerous mass is removed, sparing the rest of the breast. A radical prostatectomy is like a mastectomy because the entire prostate is removed.

We are very good at diagnosing prostate cancers, yet we're not good at knowing which ones to treat and which ones to leave alone. Prostate cancer is a slow-growing disease, so most men die with the disease rather than from it. But most men are not comfortable knowing they have cancer in their body and leaving it there. They want it out. If you look at the rate of active surveillance between 1990 and 2006, you'll see that it actually decreased. [See "Trends in prostate cancer treatment," at left.] So, in spite of the fact that we are catching a lot of cancer earlier

Trends in prostate cancer treatment

Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary Trends in Low-Risk Prostate Cancer: Risk Assessment and Treatment. *Journal of Urology* 2007;178:S14-19. PMID: 17644125.

PubMed See page 136.

Getting specific

When describing clinical tests, doctors and researchers often use the terms sensitivity and specificity. Sensitivity is how well the test identifies a disease or condition in people who have it. Specificity is how well the test identifies those who do not have a disease or condition.

**Editor's note: The terms targeted focal therapy, targeted therapy, and focal therapy are used interchangeably in this article.*

on, cancers that we might want to watch rather than treat, the number of men pursuing active surveillance is dropping. Most men don't want to sit on a cancer and most doctors don't want to sit on it either, so active surveillance often doesn't enter the discussion.

Right now, the best way to detect prostate cancer is with the PSA test, but there's another test that's being investigated, called PCA3. It seems to complement the PSA. PCA3 is a noncoding messenger RNA that is pretty specific for prostate cancer. We've done a large study of almost 2,000 men, and found that PCA3 screening complements PSA—it enhances the specificity of PSA. [See "Getting specific," page 94.] If a person has cancer, PCA3 also reflects the volume of cancer. In the future, PCA3 might help us better screen for prostate cancer and help us determine which men with the disease really need to be treated. Until then we don't really have a good solution. That's why I find targeted therapy so appealing.

How do you treat just the tumor?

With cryotherapy. It involves freezing cancer cells with argon gas, delivered to the prostate via a needle injected into the perineum. The doctor can guide the needle to the cancerous area and monitor treatment with real-time ultrasound images generated by an ultrasound probe in the patient's rectum. During cryotherapy, the cells are frozen and thawed at least twice. When ice crystals form, they tear the cell membranes apart. Cells may also burst during the freezing and thawing process. [For more information about cryotherapy, see page 85.]

Are there other types of targeted therapy?

Yes, but they aren't approved by the FDA; they are still experimental. One is HIFU, which stands for high-intensity focused ultrasound. HIFU sends a high amount of energy into the prostate through a probe inserted in the rectum. The energy beams, which enter the prostate at different angles, create heat at the point where they converge, damaging cells in just a few seconds. Sound waves also create vibrations in the tissues that further destroy the tumor. Because HIFU destroys only a small bit of tissue at a time, skin and noncancerous tissue remain unharmed. We use magnetic resonance imaging to view the prostate and see exactly where we are aiming the ultrasound. HIFU is not FDA-approved, so men can only have this procedure in the United States if they participate in a clinical trial. [For more information about HIFU, see page 89. For more details on targeted therapies, see "Focal therapies," page 90, and "Focal therapy for prostate cancer," at right.]

Photodynamic therapy [PDT], which has been used to treat skin cancer, shows potential as a focal therapy for the treatment of prostate cancer, too. During PDT, patients receive a photosensitizer. This is a light-sensitive chemical that accumulates in the target tissue and releases toxic, cell-killing substances when it's exposed to light. Optical fibers inserted into the prostate through catheters deliver the light [see Figure 17]. Newer, experimental photosensitizers seem to destroy tumors primarily by attacking the blood vessels that feed them.

Another still-experimental treatment for prostate cancer is called NanoKnife. In this procedure, two needles are inserted into the cancerous part of the prostate. An electrical current travels through and between the needles, killing the cancer. I hope to soon start working on a study using the NanoKnife and mapping biopsies.

What is a mapping biopsy?

To formally diagnose cancer, a urologist will do a biopsy, which involves taking several bits of tissue, or cores, from different parts of the prostate, examining them under a microscope, and determining whether cancer is present. If cancer is present, a traditional biopsy will tell you roughly where the cancer is located, such as the anterior right side, but you don't know exactly where it is. And because only a small number of samples are

Focal therapy for prostate cancer

Barqawi AB, Crawford ED. Emerging Role of HIFU as a Noninvasive Ablative Method to Treat Localized Prostate Cancer. *Oncology* 2008;22:123–29. PMID: 18409659.

Crawford ED, Barqawi A. Targeted Focal Therapy: A Minimally Invasive Ablation Technique for Early Prostate Cancer. *Oncology* 2007;21:27–32. PMID: 17313155.

Crawford ED, Wilson SS, Torkko KC, et al. Clinical Staging of Prostate Cancer: A Computer-Simulated Study of Transperineal Prostate Biopsy. *BJU International* 2005;96:999–1004. PMID: 16225516.

PubMed See page 136.

PHYSICIAN INTERVIEW: TARGETED FOCAL THERAPY, *continued*

taken, a cancer could be missed. For targeted therapy to work, you can't rely on a traditional biopsy. You have to have a mapping biopsy to know that you aren't missing small yet significant cancers.

To do a mapping biopsy, we use a template [see Figure 18] that was created to give patients brachytherapy, a type of radiation therapy. We take anywhere from 30 to 90 cores, depending on the size of the man's prostate, and record the precise location of each. Then we test the tissue, correlating the pathologic findings with a three-dimensional anatomical map of the prostate. Depending on the size, number, and location of any tumors, we can decide whether the patient is a candidate for targeted therapy or not.

Thirty to 90 cores—that's a lot! Do patients have any side effects?

Mapping biopsies are not without side effects. The patient has to have a catheter in for three or sometimes four days, which can lead to an inability to empty the bladder, or urinary retention, once the catheter is removed. Blood clots can also form within the bladder, blocking urine flow. Sometimes there are scrapes on the scrotum. But none of my patients have had any serious side effects. It does seem that the bigger the prostate, the worse the side effects, so I've started having men with larger prostates—those estimated to be over 50 grams—take the drug dutasteride [Avodart] for three months before we do the mapping. The drug, which is used to treat benign prostatic hyperplasia, also called an enlarged prostate, helps shrink the gland.

Who is a good candidate for a mapping biopsy?

The ideal patient for a mapping biopsy is a man who is healthy, potent, and motivated to try an alternative treatment, and has a low-volume, stage T1c cancer with a Gleason score of 6. I might also add age to that list. Many doctors believe this therapy is better for older men, but I have many patients in their 50s who are interested in it.

How accurate are mapping biopsies?

In one small study I did that will soon be published, I performed a mapping biopsy on about 30 men when they had a radical prostatectomy. Afterward, we correlated the results of the mapping biopsies with the pathology reports from the whole mounts, meaning the tissue slices from the whole prostate that the pathologist examined under the microscope after it was removed. We actually found two cancers in the mapping biopsies that were missed on the whole mounts, including a small cancer with Gleason score of 8. And the mapping biopsies didn't miss anything that was detected by the whole mounts.

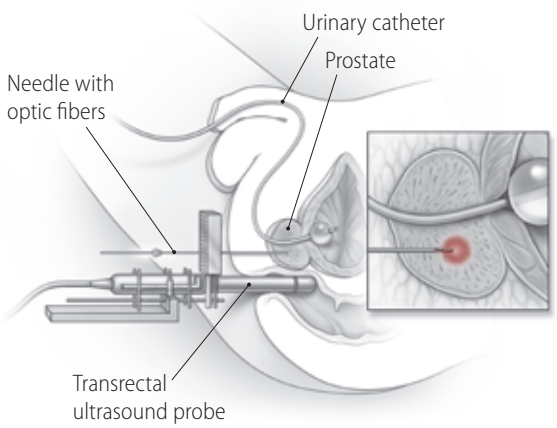
Given their level of accuracy, why aren't mapping biopsies routinely done?

They take a fair amount of time, and urologists aren't reimbursed very well for doing them. They can also lead to some minor complications. And many urologists aren't trained to do them.

What percentage of men who have a mapping biopsy could be effectively treated with targeted therapy?

I have found that about 40% of patients who have had a mapping biopsy have low-risk prostate cancers that could be treated with targeted therapy. The rest have cancer on both sides of the prostate or cancer that is more extensive or of a higher grade than first thought based on the original biopsy.

Figure 17. Photodynamic therapy



During this treatment, light-sensitive chemicals accumulate in cancerous tissue. When exposed to light from optical fibers inserted into the prostate through hollow needles, the chemicals release toxic substances that destroy tumors (inset). Doctors monitor the procedure using transrectal ultrasound.

But for the 40% who "qualify," targeted therapy could treat the cancer and limit complications like incontinence and impotence.

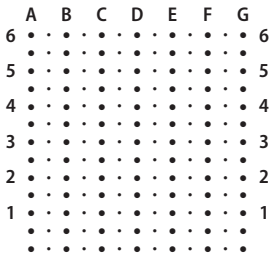
What findings on a mapping biopsy would qualify a patient for active surveillance?
The typical criteria for active surveillance apply: a small amount of low-grade, Gleason 6 cancer on one side of the prostate.

What are the challenges of targeted focal therapy?
Over the years, a lot of patients have come to me and said, "Doc, I want you to just take out part of my prostate, or treat just part of it." And I used to say, "You can't do that. This disease is multifocal—meaning it's in more than one spot in the prostate—you just can't go in and lop out part of the prostate."

But now we know that prostate cancer isn't multifocal in everybody. With mapping biopsies, we can locate the tumor or tumors and figure out exactly where treatment is needed. Down the line, there will also be better imaging tests—such as MRI or CT scans—that will allow us to really see the prostate well and see where the cancer is. We don't have that yet, unfortunately, so we have to rely on biopsies, which involve sticking a lot of needles into the prostate, and of course that isn't pleasant for the patient.

Any final comments?
Anyone who looks at the history of prostate cancer diagnosis and treatment will see that we've made a tremendous amount of progress over the past few decades. But we still don't know exactly which cancers need to be treated. Until we can do that reliably, I think we need to offer men something to control their cancer without destroying their quality of life. That's a role that targeted therapy can fill. I believe that up to 40% of currently diagnosed prostate cancers may be amenable to targeted therapy. ◆

Figure 18.
Mapping biopsy grid



Placed over the perineum, a grid like this one can aid doctors performing a mapping biopsy. Tissue samples are taken every 5 millimeters, front to back and side to side. (Each dot on the grid represents a hole through which a needle can be inserted.) This allows doctors to map the location of tumors in three dimensions and determine if a patient might be a candidate for focal therapy.

loss, one of the classic side effects of chemotherapy, occurs because the drugs damage the cells of hair follicles. Cells in the bone marrow, mouth, stomach, and intestines are also commonly affected.

Aside from hair loss, the treatment may cause fatigue, mouth sores, nausea, and infertility. The presence or absence of side effects, however, doesn't indicate how well the therapy is working. Most men find the side effects manageable, and the effects don't last very long. In a few months, the chemotherapy is finished, their bodies recover, and they steadily return to feeling normal.

The drugs (see Table 8) are given in pill form or intravenously. They are usually taken in cycles, with each period of treatment followed by a rest period. This cycle can be daily, weekly, or every three to four weeks, depending on the drug and your tolerance. Combinations of chemotherapy drugs are often more effective than single drugs, but even these combinations aren't particularly effective for advanced hormone-refractory prostate cancer.

Vaccines and other emerging therapies

Unlike vaccines that prevent infections, prostate cancer "vaccines" help fight advanced prostate cancer that no longer responds to other therapies by revving up the body's immune system. One such vaccine, sipuleucel-T

Hormones and radiation

D'Amico AV, Manola J, Loffredo M, et al. 6-Month Androgen Suppression Plus Radiation Therapy vs. Radiation Therapy Alone for Patients with Clinically Localized Prostate Cancer: A Randomized Controlled Trial. *Journal of the American Medical Association* 2004;292:821–27. PMID: 15315996.

PubMed See page 136.