

# PROSTATE CANCER: SECOND OPINION

*A Practical Guide to Understanding Management  
Options for Patients and their Families*



by  
**ANDREW L. SIEGEL, M.D.**  
Board-Certified Urologist and Urological Surgeon

An educational service provided by:  
**BERGEN UROLOGICAL ASSOCIATES**

STUART H. LEVEY, M.D. • ANDREW L. SIEGEL, M.D. • MARTIN GOLDSTEIN, M.D.

HACKENSACK UNIVERSITY MEDICAL PLAZA  
20 PROSPECT AVENUE, SUITE 715  
HACKENSACK, N.J. 07601  
201-342-6600

Cover image: *The Farnese Hercules* (Musée du Louvre)

Note: I prefer to adorn the front cover of my patient educational series with images from classical art that illustrate the sentiments expressed within. Hercules, the son of Zeus, was a great champion, a brave warrior and was renowned for making the world safer by destroying dangerous *monsters*.

# *Table of Contents*

In Shock.....	1
Dedication.....	2
Introduction.....	4
Preventative Measures.....	6
The Prostate.....	8
The Digital Rectal Examination.....	9
Prostate Specific Antigen.....	10
PSA Velocity.....	11
PSA Density.....	11
Age-Adjusted PSA.....	11
Free/Total PSA.....	12
Screening for Prostate Cancer.....	12
PCA-3 Test.....	13
Prostate Ultrasound and Biopsy.....	14
HGPIN.....	15
ASAP.....	15
Prostate Cancer.....	16
Gleason Grading System.....	17
Prostate Cancer Staging.....	18
Factors That Influence the Treatment Choices for Prostate Cancer.....	19
Prostate Cancer Treatment.....	22
Active Surveillance.....	25
Radical Prostatectomy.....	26
External Beam Radiotherapy.....	30
Conformal radiation.....	31
IMRT.....	31
Tomotherapy.....	31
Cyberknife.....	31
Proton beam therapy.....	32
Brachytherapy.....	33
High Intensity Focused Ultrasound.....	36
Cryosurgery.....	37
Androgen Deprivation Therapy.....	38
Treatment of Hormone-Refractory Prostate Cancer.....	42
Palliative Management.....	43
Future Directions.....	46
Additional Resources.....	47
About the Author.....	47

## *Shocking News—“You have prostate cancer...”*

The response to receiving the news that you have prostate cancer is often predictable, although every individual's emotional reaction is unique. The initial feelings are usually shock, disbelief, and even denial—after all, being told you have prostate cancer can be of life-changing significance. Numerous questions immediately surface: How can this be possible? Why me? Is this an error? Was my pathology report confused with another man? Can I be cured? What is my prognosis? How will treatment affect my lifestyle? Will I die soon?

*One of my patient's responses was noteworthy—in a rich Irish brogue: “Jesus Christ, I'm going to go back to drinking and smoking.”*

This response will change as you process the information over time. Most men experience discrete emotional stages as they would in any situation that could be construed as grievous or tragic. The shock is followed by anger, distress, anxiety, irritability and perhaps depression. During this period of emotional upheaval, it is common to feel fatigued, to experience difficulty concentrating, to have insomnia and to lose all interest in sex. These symptoms are all a normal part of how one processes grief.

The stage of adjustment becomes gradually manifest over time as the realization occurs that there are excellent options and treatments available, and that most men are able to live a long and healthy life after being diagnosed with prostate cancer. Ultimately, there is recognition that the problem is indeed remediable, and one comes to terms and accepts the situation and the difficult decisions that will need to be made.

## *Dedication*

This booklet is dedicated to you—the man who has been diagnosed with prostate cancer—and your family, friends, and others who support you and are seeking to help you. This educational monograph was written for you with the intent of providing a practical resource regarding the management choices available for prostate cancer. It is also appropriate for the man who has been found to have an elevated PSA blood test or an abnormal digital rectal exam, or anyone curious and interested in learning something about prostate cancer. The most important message I have to convey is that the vast majority of men who are diagnosed with prostate cancer can be optimistic and hopeful about their prognosis.

I was motivated to write this because of the need for such a resource, collated together in one comprehensive yet succinct, pragmatic and accessible unit. Prostate cancer has such a highly variable natural history and there are an absolutely bewildering variety of treatment options available, engendering a great deal of confusion for the individual grappling with trying to determine how he should best be treated. The intent of this monograph is to empower you with the knowledge and information to help navigate you through the potential management options, offering sensible and practical advice based upon my knowledge and experience, in as impartial a means as is possible.

From my perspective, the best patient is an educated patient. The decision-making process with respect to what is the best treatment option for you can be a challenging and daunting task, especially insofar as there are usually several competing options. My goal is *not* to prescribe precisely what approach to take, nor is it to proscribe what approach not to take; rather, it is to provide a working knowledge of the current state of affairs regarding prostate cancer treatment that hopefully will help enable you to make an intelligent and informed decision about the management option that is best for *you*, insofar as illness is individual and each person is unique. Armed with this information, you will be better able to work with your doctors to help find the treatment pathway that is optimal for you.

Importantly, prostate cancer is a remarkably heterogeneous disease with every single case being unique—literally as different as snowflakes—thus, the management of prostate cancer must be individualized. The major challenge for those of us who treat prostate cancer is to distinguish between clinically significant and clinically insignificant disease and to decide the best means of eradicating clinically significant disease to maintain both quantity and quality of life.

I believe that being educated and knowledgeable about prostate cancer will enable you to make the most prudent decision with respect to treatment.

I also believe in a *multi-disciplinary health care team approach* to prostate cancer. In addition to the urologist, the physicians who specialize in prostate cancer are the *radiation oncologist* and the *medical oncologist*. This trio may be considered the *prostate cancer team* and are a powerful combination in terms of their ability to educate and guide the management of a patient with prostate cancer. It is prudent to seek the consultation of a radiation oncologist and a medical oncologist, as well as a second opinion from another urologist in order to obtain the full spectrum of advice available. On the subject of radiation oncologists, at this juncture, I would like to thank Dr. Glen Gejerman for his efforts in reviewing and editing the radiation therapy section of my manuscript.

There are certainly inherent biases that physicians have in terms of their advice and opinions that are directly related to their training—in general, the urologist is quite enamored with surgery, the radiation oncologist is very fond of radiation therapy, and the medical oncologist often promotes chemotherapy. I have made a great personal effort over the past decade to transcend my surgical background and training, check my personal biases and look at the big picture in order to give honest, candid and appropriate advice to my patients. I strongly believe in the **FBSU test** (**F**ather, **B**rother, **S**on, **U**ncle test)—giving my patients the same advice I would give to my family members. In fact, when a physician recommends you undergo any kind of treatment, always ask them if they would suggest the same treatment for themselves or their own family member.

**Andrew L. Siegel, M.D.**

*“Appropriate treatment implies that therapy be applied neither to those patients for whom it is unnecessary nor to those for whom it will prove ineffective. Furthermore, the therapy should be that which will most assuredly permit the individual a qualitatively and quantitatively normal life. It need not necessarily involve an effort at cancer cure. Human nature in physicians, be they surgeons, radiotherapists, or medical oncologists, is apt to attribute good results following treatment to such treatment and bad results to the cancer, ignoring what is sometimes the equally plausible possibility that the good results are as much a consequence of the natural history of the tumor as are the bad results.”*

Willet Whitmore, M.D., 1973

(Dr. Whitmore served as chief of urology at what is now Memorial Sloan-Kettering Cancer Center and died in 1995 of prostate cancer.)

## *Introduction*

Prostate cancer is the most common non-skin malignancy among men in most western populations (186,320 new cases in 2008 in the U.S.), and is the second leading cause of cancer death among U.S. men (approximately 28,660 men in 2008). To put this in perspective, cardiovascular disease causes more than 800,000 deaths per year in American men and is the leading cause of death in men with prostate cancer—the point being that many more men die of heart disease than of prostate cancer, and even in the population of men with prostate cancer, many more men die *with* it than of it.

The three major risk factors for prostate cancer are *age*, *race*, and *family history*. The likelihood of developing prostate cancer increases with the aging process, thought to be on the basis of gradual accumulation of DNA mutations due to incremental oxidative damage (literally “rusting”) of prostate cells. With each decade of aging, the incidence of prostate cancer increases appreciably.

In terms of race, African American men have the highest reported incidence of prostate cancer in the world, with an incidence of 1.6 times that of Caucasian men in the United States; additionally, mortality is 2.4 times higher for African American men. On a worldwide basis, the highest incidence is in North America and Scandinavia and the lowest incidence is in Asia.

Prostate cancer tends to run in families, so it is prudent for male children of those with prostate cancer to be checked on an annual basis starting at age 40 (with a PSA blood test and digital rectal exam). With respect to familial prostate cancer, risk increases according to the number of affected family members (the more affected, the higher the risk), their degree of relatedness (brother and/or father affected confer a higher risk than cousin and/or uncle), and the age at which they were diagnosed (relatives of patients diagnosed younger than 55 years old are at highest risk). Generally speaking, if you have a brother or a father with prostate cancer, your risk of developing it is doubled. If you have three family members with prostate cancer, or if the disease occurs in three generations in your family, or if two of your first degree relatives have been diagnosed at an age younger than 55 years, then you have a good likelihood for *hereditary prostate cancer*, which confers a 50% risk of developing the disease.

To date, eight prostate cancer susceptibility genes have been discovered—although not of great clinical relevance at this time, these genes show great promise and potential for the future.

*My father, a retired urologist, was diagnosed with prostate cancer at age 65 and is currently 77 years old and thriving. For this reason, I have been very diligent in seeing my internist annually for a prostate examination and a PSA blood test. Additionally, I have been proactive in taking a medication—to be discussed in detail later—to decrease my risk of prostate cancer. My associate, Dr. Martin Goldstein, takes the same medication insofar as his father was diagnosed with prostate cancer at age 57.*

Prostate cancer is unique among solid tumors in that it exists in two forms: a *latent* form (evident on autopsy studies, but not causing an abnormal rectal exam or PSA), which is present in 60-70% of men older than 80; and a *clinically evident* form (causing an abnormal rectal exam or elevated PSA), which affects approximately 1 in 6 men in the United States. Overall, men have an approximately 17% chance of being diagnosed with prostate cancer and a 3% chance of dying from it. This high ratio of prostate cancer *incidence to mortality* suggests that a portion of the cancers are minimal or indolent, non life-threatening conditions.

In 2009, most prostate cancers are detected on the basis of a PSA elevation ranging from 2.5-10 ng/ml. Widespread PSA testing has resulted in the increased diagnosis of prostate cancer and a downward stage migration to non-palpable, organ-confined cancer with a parallel reduction in mortality—as opposed to the pre-PSA era, when most cancers were detected on the basis of a palpably abnormal digital rectal exam and were at a more advanced stage at presentation.

Are you ready for some good news? It is very important to know that when detected early, prostate cancer is highly curable. In the USA, more than 90% of men diagnosed with prostate cancer survive at least 10 years after the diagnosis is made. Even when not discovered early, it is a very manageable condition. In general terms, prostate cancer is a relatively slow-growing process. In fact, as already mentioned but worthy of repeating, many men will not die *from* it, but *with* it. Although most prostate cancers diagnosed at an early stage often have an indolent course, local tumor progression and metastases may certainly develop in the long term; therefore, early treatment is an important consideration for men with a general life expectancy exceeding 10 years.

Localized prostate cancer typically causes no symptoms whatsoever and is typically diagnosed by a biopsy done because of a PSA elevation, an accelerated increase in the PSA over time, or an abnormal digital rectal examination. Non-palpable cancers, i.e., those picked up by virtue of a PSA elevation or accelerated PSA velocity, now account for 75% of all newly diagnosed prostate cancers. Although screening for prostate cancer remains somewhat controversial because of a lack of studies demonstrating a decrease in mortality in screened populations, the observed trends in PSA-driven detection of prostate cancer at earlier stages and declining mortality where screening is common provide strong inferential evidence that screening is beneficial.

### *Preventative Measures*

Wouldn't it be wonderful if we could prevent the occurrence of prostate cancer! It certainly would make my job a whole lot easier. Unfortunately, we are not there yet—but we do know a thing or two about lifestyle measures that can be pursued to maintain your health in general and to help mitigate your chances of developing prostate cancer.

When Asian men, who have the lowest incidence of prostate cancer, migrate to western countries, their risk of prostate cancer increases over time. Clearly, a coronary-clogging western diet high in animal fat and highly processed foods and low in fruits and vegetables is associated with a higher incidence of many preventable problems including cancer. Americans, in fact, consume an average of nearly two pounds per day of animal products.

A heart-healthy, colon-healthy diet is a prostate-healthy and life-healthy diet. This, combined with a healthy lifestyle, will afford you your best opportunity at minimizing heart disease, diabetes, and a host of cancers. This means weight management; the avoidance of obesity; healthy eating with abundant fruits and vegetables (chock full of antioxidants, vitamins, minerals and fiber) and *real* food as opposed to processed foods; consumption of animal fats and dairy in moderation; avoidance of tobacco and excessive alcohol; and plenty of exercise. And if you do develop prostate cancer, you will be in great physical shape and will heal that much better from any intervention necessary to treat the prostate cancer. Good nutrition and exercise helps in part by inhibiting oxidation and inflammation, factors that contribute not only to prostate cancer but also to conditions such as heart disease and osteoarthritis.

Michael Pollan, a journalism professor at the University of California, Berkeley and author of *The Omnivore's Dilemma*, summarized in a most succinct way the answer to the question of what humans should eat, in his seven words: **“Eat food. Not too much. Mostly plants.”** By *food*, he means a nutritional substance that your grandmother would recognize as food, not a *food-like* highly processed substitute. *Not too much* is pretty obvious. A *mostly plants*-based diet will result in the consumption of a moderate amount of calories and plenty of fiber and anti-oxidants.

In addition to recommending a regimen of healthy eating and regular participation in exercise, there are medications that can help prevent the occurrence of prostate cancer. The presence of precursor lesions such as high grade prostate intraepithelial neoplasia (HGPIN) many years before the onset of prostate cancer, coupled with the increasing prevalence of prostate cancer with the aging process, suggest that the process of developing cancer takes place over a protracted interval of time. In fact, it is estimated that it takes many years—often more than a decade—from the initiation of the initial mutation to the time when prostate cancer becomes clinically manifest with either a PSA elevation or an abnormal digital rectal examination. In theory, this provides the opportunity for intervention before the establishment of a cancer.

The Prostate Cancer Prevention Trial was a clinical trial that tested whether *Finasteride*, which induces a deficiency of the enzyme *5-alpha reductase*, would prevent prostate cancer. This trial was based upon the fact that prostate cancer does not occur in the absence of testosterone and that men with a congenital absence of 5-alpha reductase (that functions to convert testosterone to the activated form, *dihydro-testosterone*) do not develop benign or malignant prostate growth. This 7-year study involved almost 20,000 men who were randomly assigned to Finasteride or placebo. **The study was terminated 15 months early because a 25% risk reduction for prostate cancer was achieved on Finasteride.** The other finding was that the prevalence of higher-grade cancers was slightly higher in the Finasteride group (6.4% vs. 5.1%); however, Finasteride is known to change the pathological appearance of the prostate in such a way as to make determination of an accurate grade difficult. (Recent trial results indicate that prophylactic use of Finasteride is not linked to the development of more aggressive tumors.) Prostates in those treated with Finasteride were 25% smaller at the end of the study as opposed to prostates in the placebo group.

*At the time of my ten-year medical school reunion, I noticed that the hair on my crown was thinning. I did not give it another thought until a number of years later, when I received the disheartening news from my wife and father that I had sunburn on my crown! Oh no—this did not appeal to my sense of vanity at all! I tried topical Minoxidil (Rogaine) but it was ineffective, so I started taking Propecia (a.k.a. Finasteride) every morning. Lo and behold, my exposed pate filled in and ultimately I had a full re-growth of hair.*

*When the Prostate Cancer Prevention Trial report came out revealing a 25% risk reduction for prostate cancer associated with the use of Finasteride, this cinched it—particularly insofar as my father had been diagnosed with prostate cancer at age 65. Finasteride is a drug that fixes my bald spot, shrinks my prostate, and helps prevent prostate cancer, for which I have a family history. It seemed like a win-win situation, a no-brainer! I will share with you a little insider information—there are many urologists and other physicians who avail themselves of this class of medication.*

**Bottom line: Finasteride (Proscar and Propecia) and the other medication of its class, Dutasteride (Avodart), have the benefits of helping to prevent prostate cancer, shrinking the prostate gland, lowering the PSA, mitigating symptoms of prostate obstruction, and growing hair on your scalp.** That is one winning combination as far as I am concerned and I happily swallow my daily dose every morning. These medications will lower the PSA by 50%, so any man taking this class of medication will need to have his PSA multiplied by two in order to obtain the actual PSA. If the PSA does not drop, or if it goes up while on this class of medication, it is suspicious for occult prostate cancer.

## *What is the Prostate?*

The prostate is a reproductive gland that functions to manufacture a milky fluid that serves as a nutrient vehicle for sperm. Similar to the breast that manufactures milk, the prostate is a powerful little factory that produces this fluid, which is released during ejaculation as a component of the semen. During orgasm, muscles within the prostate gland squeeze the prostatic secretions into the urethra, where they mix with sperm from the testes and secretions from the seminal vesicles, structures located behind the bladder that produce the bulk of the volume of the semen.

The prostate is anatomically situated behind the pubic bone, deep in the pelvis atop the rectum, at the outlet to the bladder. Urine and semen must pass through the prostate in order to exit the urethra. The prostate is attached to the bladder above and the urethra below, and is surrounded by sphincters responsible for urinary control. The prostate circumferentially envelops the urethra, a position that allows the ducts of the gland to drain into the urethra. The prostate is surrounded by a veil of tissue known as the capsule. A young man's prostate is about the size of a walnut, but under the influences of aging, genetics and testosterone, the prostate can increase substantially in size. As it does so, it can compress and obstruct the urethra, giving rise to annoying lower urinary tract symptoms.

Since the prostate is nestled deep within the male pelvis in a strategic location at the bladder outlet and is situated at the crossroads of the urinary and reproductive tracts, I like to think of it as a man's *center of gravity*.

*I confess that I really like having my center of gravity intact—just the way it is—and I am in no way enamored with the thought of having it manipulated, tweaked, disturbed or messed with in any way.*

## *What is a Digital Rectal Examination (DRE)?*

Sorry to disappoint you, but this is not a fancy and sophisticated, high-tech *digital* (vs. analog) test, but a good old-fashioned index finger (digit) up the rectum! This is an important part of the male physical exam in which a gloved, lubricated finger is used to feel the surface of the prostate gland via the rectum. Although this is not a pleasant examination, generally speaking, it is more awkward and uncomfortable than painful, and is very brief, usually taking only 30 seconds or so. I don't like giving this exam any more than you like receiving it, but it is important because it provides essential information that cannot be derived by any other means.

If the prostate has an abnormal hard spot or bump, or simply feels uneven, it may be a sign of prostate cancer. Our hand can provide a good means of understanding what we are feeling for. Turn your hand so that the palm is in an upwards-facing direction. The normal prostate feels like the spongy, muscular, fleshy tissue at the base of our thumb, whereas cancers feel hard, like the knuckle of our thumb.

The DRE in conjunction with the PSA test are the two best means of screening for prostate cancer. When the DRE and the PSA are

used as screening tests for prostate cancer, the detection rates are higher with PSA than the DRE, but highest with a combination of the two tests since they are complementary. It should be noted that the pathological features of prostate cancers detected on the basis of an abnormal DRE are, in general, less favorable than those of cancers detected by a PSA elevation. In other words, if the cancer can be felt, we tend to worry more about it than if it cannot be felt.

### *What is the PSA Test?*

Prostate-specific antigen (PSA) is a protein produced by the cells of the prostate gland. More specifically, it is an enzyme known as a *protease* that functions to liquefy semen following ejaculation.

The PSA test measures the level of PSA in the blood and is the best tool currently available for detecting prostate cancer in its earliest—and most curable—stages. Although PSA is widely accepted as a tumor marker, it is prostate *organ-specific* but not *cancer-specific*. In other words, PSA can be elevated due to the presence of prostate cancer; however, not all elevated PSA tests mean that prostate cancer is present—benign prostate conditions can elevate it as well; the most common of these are *prostatitis* (inflammation of the prostate) and *benign prostatic hyperplasia* (*BPH*, an enlargement of the prostate gland).

Prostate cancer cells do not make more PSA, but rather less PSA than normal prostate cells. The elevated PSA that is detected in the blood associated with prostate cancer occurs because of a disruption of the cellular architecture of the prostate cells, the loss of this barrier of which permits the leakage of PSA into the circulation. In similar fashion, this egress of PSA from disrupted prostate epithelial cells can occur in the setting of BPH, prostatitis, and prostate manipulation (a vigorous prostate examination or a prostate biopsy).

The PSA test is extremely helpful to monitor patients with a history of prostate cancer to check the status of the cancer. If the PSA level begins to rise, it may be the first sign of recurrence. Such a biochemical relapse typically precedes clinical relapse by months or years. However, a single elevated PSA level in a patient with a history of prostate cancer does not always mean the cancer has come back. A trend of rising PSAs over time is much more valuable than is a single elevated PSA.

Refinements in PSA testing include the following:

**PSA velocity:** It is very useful to compare the PSA values from year to year. Generally, the PSA will increase by only a small increment, reflecting benign prostate growth. If the PSA accelerates at a greater rate than anticipated—a condition known as accelerated PSA velocity—an ultrasound/biopsy is indicated. A PSA velocity > 0.75 ng/ml in one year is suggestive of prostate cancer.

**PSA density:** PSA density (level of PSA divided by the volume of the prostate) considers the relationship of the PSA level to the size of the prostate. In other words, an elevated PSA might not arouse suspicion if you have a very enlarged prostate. A PSA density > 0.15 is suggestive of prostate cancer.

**Age-adjusted PSA:** Age is an important factor with respect to PSA levels. It is now recognized that PSA will increase with the aging process in accordance with the increasing size of the prostate gland that occurs with growing older. For this reason, age-adjusted PSA levels can be useful to determine when further diagnostic tests are needed.

Age (years)	PSA Upper Limit (ng/ml)	Age (years)	PSA Upper Limit (ng/ml)
40	2.0	60	3.8
41	2.1	61	4.0
42	2.2	62	4.0
43	2.3	63	4.2
44	2.3	64	4.4
45	2.4	65	4.5
46	2.5	66	4.6
47	5.6	67	4.7
48	2.6	68	4.9
49	2.7	69	5.1
50	2.8	70	5.3
51	2.9	71	5.4
52	3.0	72	5.6
53	3.1	73	5.8
54	3.2	74	6.0
55	3.3	75	6.2
56	3.4	76	6.4
57	3.5	77	6.6
58	3.6	78	6.8
59	3.7	79	7.0

**Free/Total PSA:** Essentially, PSA circulates in the blood in two forms: a “free” form in which the PSA is unbound to any other structures, and a “complex” PSA in which the PSA is bound to a protein. The free PSA/total PSA ratio can offer a predictive value, in similar fashion to the way the HDL cholesterol/total cholesterol can be helpful in a man with an elevated cholesterol level. It has been found that in men with an elevated PSA, the free to total PSA ratio can enhance the specificity of PSA testing for the diagnosis of cancer. In general, the higher the free to total PSA, the greater the probability that benign enlargement of the prostate is the underlying source of the PSA elevation. In men with a PSA between 4.0 and 10.0, the probability of cancer is only 8% if the ratio is greater than 25%; however, the probability of cancer increases to 56% if the ratio is less than 10%.

Free PSA/ Total PSA	% Probability of Cancer
> 25%	0-10 %
20-25%	16%
15-20%	20%
10-15%	28%
0-10%	56%

### *Screening for Prostate Cancer*

Two controversial studies were published in the New England Journal of Medicine in March 2009 regarding screening for prostate cancer. The results were summarized on the front pages of many newspapers, resulting in confusion for many patients. Andriole et al in the USA reported no mortality benefit from combined digital rectal exam and PSA screening after 7-10 years. Schroeder et al in Europe reported that PSA screening alone (without rectal exams)

resulted in a 20% decrease in the death rate at a median follow up of 9 years. It is the consensus of many urologists that these studies were published prematurely, with ambiguous results.

The hard facts:

- 95% of male urologists and 80% of primary care physicians older than 50 have PSA screening—clearly those in the know feel that screening is beneficial.
- USA death rates from prostate cancer have fallen 4% annually since 1992, five years after introduction of PSA testing.
- Many urologists do not screen or treat men who have a life expectancy less than 10 years for the very reason that prostate cancer rarely causes mortality in the first decade after diagnosis and that other competing medical issues will cause death before the prostate cancer has a chance to.
- Prostate cancer is a slow-growing process and early detection and treatment is directed at extending life well beyond the decade following diagnosis!
- These two studies will not prove meaningful until carried out for 15, 20, 25 years and beyond—the time reference in which we expect treatment to make a meaningful difference.

Another controversial subject is at what age to stop screening for prostate cancer. According to the United States Preventative Services Task Force update, the “harms of screening outweigh the benefits in men 75 years old or older.” Studies have shown that at age 75 if you have a PSA less than 3.0 ng/ml, the chances of later developing high-risk prostate cancer are minimal. My opinion is that all 75-year-olds are not the same, functional age trumps chronological age, and that an individual’s preference regarding screening is of great importance.

### *What is the PCA-3 Test?*

**PCA-3 (Prostate Cancer Antigen-3)** is a gene that exists in the nucleus of prostate cells. It is a specific type of RNA (ribonucleic acid) that is released in high levels by prostate cancer cells that has proven to be useful as a marker for prostate cancer. PCA-3 expression is 60-100 fold greater in prostate cancer cells as compared to benign prostate cells, conferring upon this gene a specificity that is lacking with the PSA.

The PCA-3 test is a urine test that does not require a sample of blood. The prostate is gently massaged via a digital rectal exam, in order to push some prostate cells into the urethra. The first ounce of urine voided immediately after such a massage is rich in prostatic fluid and cells and is collected and assayed for the quantity of PCA-3 genetic material. Urinary levels of PCA-3 are not affected by prostate enlargement or inflammation, in contradistinction to PSA levels.

## *What is a Prostate Ultrasound and Biopsy?*

If there is concern or suspicion for prostate cancer—i.e., an abnormal digital rectal exam, an elevation in PSA, or an accelerated PSA velocity, the definitive diagnostic test is an office procedure known as an *ultrasound-guided prostate biopsy*. Prostate ultrasound is an effective means of imaging using sound waves (like a sonar on a submarine) that are generated by an ultrasound probe placed in the rectum. Reflected echoes create a high-resolution image of the prostate to check for abnormalities, measure the volume of the prostate, and guide the prostate biopsies. The ultrasound image alone is not sufficient to diagnose prostate cancer without a tissue biopsy.

Preparation for the prostate ultrasound and biopsy involves discontinuing anti-coagulant medications and blood thinners for a week or so prior to the procedure. It is imperative that a Fleet's enema be performed the night before the biopsy in order to cleanse the rectum. It is also vital that antibiotics be taken prior to and after the biopsy since the biopsies are performed via the rectum. An oral sedative one-hour before the procedure is useful to both allay anxiety and relax the anal sphincter.

In the knee-chest position while lying on your side, the ultrasound probe is placed gently into the rectum. After obtaining careful imaging in two planes and volume measurements, local anesthetic is injected so that prostate biopsies can be taken with minimal discomfort. The biopsy cores are obtained with a spring-driven needle device that is passed through the needle guide attached to the ultrasound probe. Generally, a dozen biopsies are obtained—six from each side with two biopsies each from the apex, mid-gland and base, providing a pathological “map” of the prostate. If any abnormality is visualized on ultrasound—classically a *hypo-echoic region* (*an area with less echoes than adjacent prostate tissue*)—this specific area will be

biopsied as well. Each biopsy is placed in a separate specimen container noting the site of the biopsy and is carefully examined by a skilled pathologist in order to make a diagnosis.

On occasion, a *saturation biopsy* is done, in which 20 or more cores are obtained.

After the biopsy, it is important to stay well hydrated and to take it easy for a day or so. Blood in the urine, stool, or semen is common after the biopsy and should not be a reason for concern.

## *What Will My Biopsy Report Tell Me?*

There are four possible outcomes of the prostate biopsy:

- **Benign**
- **HGPIN (High Grade Prostate Intra-epithelial Neoplasia)**
- **ASAP (Atypical Small Acinar Proliferation)**
- **Prostate Cancer**

### *What is HGPIN?*

HGPIN is an acronym for **H**igh **G**rade **P**rostate **I**ntra-epithelial **N**eoplasia. The incidence of HGPIN on needle biopsy is between 5% and 8%. Essentially, HGPIN is an abnormality seen under the microscope that is considered to be a pre-malignant precursor lesion to prostate cancer. The risk for cancer following the diagnosis of HGPIN on needle biopsy is 24%. It is recommended that men who are found to have HGPIN have a repeat biopsy approximately one year following the diagnosis of HGPIN. The more cores containing HGPIN on the initial prostate biopsy, the greater the likelihood of cancer on subsequent biopsies.

### *What is ASAP?*

ASAP is an acronym for **A**typical **S**mall **A**cinar **P**roliferation. About 5% of needle biopsy pathology reports are diagnosed with this, an abnormality seen under the microscope that is suspicious for prostate cancer, but falls below the diagnostic threshold. The risk for cancer following the diagnosis of ASAP on needle biopsy is approximately 40%. All men with an atypical diagnosis should undergo re-biopsy within 3 to 6 months.

## *What is Prostate Cancer?*

In general terms, cancer infers *out-of-control growth of abnormal cells*. Whereas normal cells grow, divide and die in an orderly fashion, cancer cells continue to grow, divide and form new abnormal cells. Cancer cells develop because of damage to DNA, which provides the blueprint for activities in all cells. Under usual circumstances, the body is able to repair damaged DNA, but with cancer cells, the damaged DNA is not repaired.

Prostate cancer is usually an **adenocarcinoma**—a type of malignancy that originates from glandular cells. Cancer happens with the occurrence of a **mutation**—a permanent change in the DNA sequence of a gene—allowing abnormal cells to divide and proliferate abnormally and without control. This unregulated cellular growth has the potential for invasion of adjacent tissues and spread to other areas of the body. Damaged DNA can be inherited, although it is much more common for DNA to be damaged by exposure to an environmental toxin or on the basis of random cellular events.

On occasion, the prostate cancer is a **small cell carcinoma**—a type of malignancy that originates from neuro-endocrine cells. It accounts for about 1% of prostate cancers. It is a high-grade and aggressive cancer that is typically diagnosed at an advanced stage. It usually does not respond to androgen deprivation therapy (see page 38) and tends to progress rapidly with a poor prognosis and an average survival of under one year.

If your biopsy demonstrates prostate cancer, the pathologist will provide a detailed report indicating the following:

- The number of cores showing cancer
- The percent of each core showing cancer
- The location of the cores harboring cancer
- The grade of the cancer, a.k.a. the **Gleason score**
- A “map” of the biopsies

## What is the Gleason Grading System?

Dr. Gleason (deceased January 2009) devised a very important and seminal prostate cancer scoring system through observations of the cellular architecture of prostate cells under the microscope. He recognized that prostate cancer *grade* was the most reliable indicator of the potential for cancer growth and spread. His legacy, the grading system that he devised and that bears his name—the *Gleason score*—provides one of the best guides to the prognosis and treatment of an individual case of prostate cancer.

The grade is based on a pathologist's microscopic examination of prostate tissue that has been chemically stained after a biopsy. Essentially, grade is an indication of the extent of difference in appearance that cancer cells have as compared with normal cells. In other words, the grade depends on how far the cells deviate from normal appearance. Low-grade cancers generally appear rather similar to normal cells whereas high-grade cancers have little resemblance to normal cells.

PROSTATIC ADENOCARCINOMA  
(Histological Patterns)



Cancer cells can show various patterns. To determine a Gleason score, a pathologist assigns a separate numerical grade to the two most predominant architectural patterns of the cancer cells. The numbers range from 1 (the cells look nearly normal) to 5 (the cells have the most cancerous appearance). The sum of the two grades is the Gleason score. The lowest possible score is 2, which rarely occurs; the highest is 10.

The Gleason score can predict the aggressiveness and behavior of the cancer. High scores tend to suggest a worse prognosis than lower scores because the more deranged and mutated cells usually grow faster than the more normal-appearing ones. Prognosis also depends on further refinements. For example, a score of 7 can occur two ways: 4 plus 3 or 3 plus 4. With 4 plus 3, cancer cells in the most predominant category appear more aggressive than those in the secondary pattern, suggesting a more serious threat than a 3 plus 4 score, in which cells in the most predominant group appear only moderately aggressive.

Prostate cancers can be “triaged” into one of three groupings based upon Gleason score. Scores of 2 through 4 are considered low grade; 5 through 7, intermediate grade; 8 through 10, high grade. Generally speaking, low score Gleason 2-4 cancers will often fare well regardless of treatment, high score Gleason cancers 8-10 may fare poorly regardless of treatment, and the intermediate group score 5-7 often have the greatest potential to be converted from a potential problem to a cure with appropriate treatment.

## *How is Prostate Cancer Staged?*

Once the diagnosis of prostate cancer is made, the next step is **staging**—testing to see the extent of disease. In addition to DRE and PSA the following tests may be used to stage prostate cancer:

**Sonography** to image the upper urinary tracts and ensure absence of urinary obstruction.

**Cystoscopy** to assess prostatic obstruction and ensure absence of bladder base involvement or other bladder pathology.

**Bone Scan** to assess the bony skeleton for spread; this can often be avoided when the PSA is less than 20 ng/ml.

**Computerized Tomography** and/or **Magnetic Resonance Imaging** to image the prostate gland and adjacent structures including seminal vesicles and lymph glands; these tests can often be omitted when the PSA level is not significantly elevated.

The **TMN (Tumor/Metastases/Lymph Nodes)** system more precisely delineates the staging as follows:

### **Stage T1**

Tumor is microscopic and confined to the prostate but is undetectable by a digital rectal exam (DRE). The tumor is detected by virtue of a PSA elevation prompting a biopsy.

### **Stage T2**

Tumor is confined to the prostate and can be detected by DRE.

T2a involves less than half of one prostate lobe. T2b involves more than half of one lobe. T2c involves both lobes.

### **Stage T3 or T4**

Stage T3 tumors have spread to tissue adjacent to the prostate or to the seminal vesicles. Stage T4 tumors have spread to organs near the prostate, such as the bladder.

## Stage N+ or M+

Cancer has spread to pelvic lymph nodes (N+) or to lymph nodes, organs, or bones distant from the prostate (M+).

### *What are the Factors That Influence the Treatment Choices for Prostate Cancer?*

Prostate cancer can be sub-divided into three groups: **localized**—the cancer is confined within the prostate gland; **locally advanced**—the cancer has spread beyond the prostate to surrounding tissue and possibly the lymph nodes; **metastatic**—the cancer has spread into remote parts of the body such as the bones.

Treatment options are predicated upon the following factors: **age and life expectancy, general health status, PSA level, Gleason score, stage, number of involved biopsies and the percentage of each core involved, urinary symptoms and personal preferences.**

**Age and life expectancy:** The prevailing theme accepted among experts is that the more years you potentially have to live, the greater the likelihood that radical prostatectomy (surgical removal of the entire prostate gland) will provide you the greatest chance of achieving that potential. So, if you are 43 year old and in perfect health, the most prudent option is often a radical prostatectomy. On the other hand, if you are elderly and have a less than ten-year life expectancy, you may not need any treatment as other more pressing issues may cause your demise before the prostate cancer has a chance to. With regards to age, I am referring to *physiological age* as opposed to *chronological age*—that is, not how many years per se that you have lived on the planet, but at what age you are functioning. Of two men who are chronologically 65 years old, one may be functioning like a 55 year old and the other an 80 year old, and the treatment needs to be tailored accordingly.

As surgery and radiation are competitive options in terms of 15-year results, and the morbidity and side effects of surgery are greater than that of radiation, at a certain age radiotherapy becomes a prudent consideration.

**Health status:** If you are not in good health, and do not have an expected ten-year life expectancy, there is usually no compelling reason to treat the prostate cancer as other health issues are likely to be of more concern than the prostate cancer.

In general, surgery should be reserved for healthy men who can tolerate an invasive surgical procedure and the general anesthesia necessary to undergo it. If your health is compromised, but you have a greater than ten-year life expectancy, radiation becomes a sensible management option.

**PSA:** In general, the lower the PSA, the greater the chance of localized (organ-confined) cancer and conversely, the higher the PSA, the greater the chance of non-localized cancer. Since the intent of surgery or brachytherapy (seed implant radiation) is cure of the disease, the lower the PSA, the greater the likelihood of cure. Men with a PSA greater than 20 will have a higher risk of locally advanced or metastatic disease, and will have a greater likelihood of failing surgery or brachytherapy. Therefore, efforts at cure are directed towards those most likely to be able to be cured—those with a PSA less than 20. If there is locally advanced or metastatic disease, often marked by a very elevated PSA, androgen deprivation therapy or external radiation to the tissues involved are better options than those treatments directed at localized disease.

**Gleason score:** As discussed above, the Gleason score is a very important factor that is considered prior to making an intelligent choice regarding treatment. Remember, low score Gleason 2-4 cancers will often act in an indolent fashion and fare well regardless of treatment, high score Gleason cancers 8-10 may act in an aggressive fashion and fare poorly regardless of treatment, and the intermediate group score 5-7 often have the greatest potential to be converted from a potential problem to a cure with appropriate treatment. A high Gleason score will mandate more aggressive management as a surveillance protocol would not be prudent under these circumstances.

**Stage:** As discussed above, stage is another term for *extent of the disease* and treatment is predicated upon properly determining this. Stage is determined by DRE, computerized tomography, bone scan, magnetic resonance imaging, etc.

For example, prostatectomy or brachytherapy radiation would be considered appropriate for localized disease, but not for metastatic disease. As another example, prostate cancer diagnosed because of a PSA elevation without the presence of an abnormality on DRE (a prostate nodule) may be treated differently than a prostate cancer diagnosed because of an abnormality on DRE. This is because the presence of palpable cancer (a nodule) indicates that the cancer

is already close to the capsule—perhaps beyond the capsule—whereas non-palpable cancer is typically earlier in the natural course of cancer progression and most amenable to localized treatment of curative intent.

**Number of involved biopsies and percent of each core involved:**

Generally, a dozen biopsy cores are obtained and the number of cores that harbor cancer can be valuable information to help guide treatment. A man who has 12/12 cores demonstrating cancer has a very different disease than a man with 1/12 cores showing cancer. The percentage of each core that harbors cancer can also be valuable information. A man with 6/12 cores demonstrating cancer with 100% of each of the six cores involved has a very different disease than a man with 1/12 cores harboring cancer with 5% of that core involved.

**Urinary Symptoms:** The presence of **Lower Urinary Tract Symptoms (LUTS)** can be an important factor in guiding treatment options.

**Obstructive LUTS** consist of the following:

- **hesitancy**—a stream that is slow to start
- **weak stream**—a stream that lacks force
- **narrow caliber stream**—a thin stream
- **intermittency**—a stream that starts and stops
- **straining**—the need to use abdominal muscles to void
- **prolonged emptying time**—excessive voiding time
- **incomplete emptying**—the inability to satisfactorily empty the bladder

**Irritative LUTS** consist of the following:

- **frequency**—urinating much more often than normal
- **nocturia**—awakening from sleep to urinate
- **urgency**—the sudden and strong desire to urinate
- **precipitancy**—the need to get to the toilet in a hurry
- **urgency incontinence**—the sudden and strong desire to urinate with an inability to get to the toilet in time to prevent leakage

The presence or absence of such LUTS can be an important

factor helping to guide the most appropriate treatment options. For example, if a man has significant LUTS, a prostatectomy may be the best management option in order to manage both the cancer and the annoying symptoms, as opposed to radiation therapy that has a tendency to exacerbate such symptoms, at least for the short term.

**Personal preferences:** My goal as urologist is to help educate you and navigate you through the potential management options, offering sensible and pragmatic advice based upon my knowledge and experience. My goal is **not** to dictate exactly what approach to take, as there are usually several competing management options. Again, I truly believe in the **FBSU test (Father, Brother, Son, Uncle test)**—giving my patient's the same advice I would give to such family members. Recognizing that every man has different priorities and values as well as differing concerns regarding the collateral effects of treatment choices, the opinion of the patient who has a good understanding of the management options is of paramount importance in the ultimate choice of a treatment.

## *How is Prostate Cancer Treated?*

Determination of the potential risk of prostate cancer to progress, spread, and cause mortality is important before embarking upon a specific treatment plan. A commonly used risk stratification scheme is the following:

**Low risk:** PSA <10; Gleason 6 or less; Stage T2a or less

This group of men is most likely to have localized disease and will have a 90-95% recurrence-free survival rate 5 years after radical prostatectomy, external radiotherapy, or brachytherapy.

**Intermediate risk:** PSA 10-20; Gleason 7; Stage T2b/T2c

This group of men will have a 65-75% recurrence-free survival rate 5 years after radical prostatectomy, external radiotherapy, or brachytherapy. Intermediate-risk prostate cancer has improved survival when *short-term* androgen deprivation therapy is combined with radiotherapy. Androgen deprivation therapy (ADT) usually involves an injection of a medication that suppresses testosterone, the male hormone that stimulates prostate growth.

**High risk: PSA >20; Gleason 8-10; Stage T3**

This group of men will have about a 50% recurrence-free survival rate 5 years after radical prostatectomy, external radiotherapy, or brachytherapy. Combined modality therapy is likely to be needed, such as radiotherapy plus androgen deprivation therapy, or radical prostatectomy plus adjuvant radiation. High-risk prostate cancer patients benefit when *long-term* androgen deprivation therapy is combined with radiotherapy.

The percent of cores having positive biopsies and certain findings on MRI can be used to shift some patients with intermediate risk disease into the low or high group. A high PSA velocity preceding the diagnosis of prostate cancer has been associated with a poorer prognosis and can move any patient in the low or intermediate risk group into the high-risk group.

Treatment for the purpose of ***cure of the cancer*** is done when the prostate cancer is localized to the prostate. The goal is to eliminate all prostate cancer cells from the body. If the cancer is localized to the prostate, options are surgical removal of the prostate gland (***radical prostatectomy***) and prostate radiation (***brachytherapy*** and ***external beam radiotherapy***). ***Cryosurgery*** (*freeze destruction of the prostate*) or ***High Intensity Focused Ultrasound*** (*heat destruction of the prostate*) are other approaches, albeit less traditional than surgery or radiotherapy. In general, if you are very young and in good health, the option of choice is often surgical removal of the prostate as this has been shown to be a highly effective means of long-term cure. However, radiation therapy may be an excellent alternative to surgery with competing results and often is associated with considerably less adverse effects. Another management option is ***active surveillance***, in which there is no treatment per se aside from careful monitoring with a change in strategy if monitoring indicators worsen.

The incidence of locally advanced T3-T4 prostate cancer is significantly less than it used to be in the pre-PSA era. However, it still does occur and incurs a significant risk of progression and death if untreated. Many men with T3 disease have regional spread and thus are not curative by prostatectomy; however, select patients may benefit from the local control accomplished by prostatectomy and occasionally complete excision can be accomplished. *Adjuvant* radiation therapy (radiotherapy given as soon as the healing process after prostatectomy is completed) coupled with

**androgen deprivation therapy** are useful to improve local control and reduce *biochemical recurrence* (the presence of an elevated PSA after prostatectomy). Another option for T3 prostate cancer is the combination of radiation therapy and androgen deprivation, avoiding prostatectomy entirely.

Treatment for the purpose of **palliation of the cancer** is done when the prostate cancer is advanced well beyond the confines of the prostate gland, often to bone. Here the goal is reduction in the severity of the cancer, but not cure. Androgen deprivation therapy is used in this setting.

No matter what the treatment, careful follow up is imperative. For the first year, a PSA—an excellent marker of the level of activity of prostate cancer—is typically obtained every three months, then subsequently every six months, and ultimately on an annual basis. After successful radical prostatectomy, the PSA should be at an undetectable level; after successful radiation, the PSA should revert to a very low level and remain so.

After definitive treatment, a rising PSA may be the sole manifestation of the recurrence of prostate cancer, a condition known as *biochemical recurrence*. This is an important issue since more than 50,000 American men annually are diagnosed with this. The important question that needs to be answered is whether the PSA elevation is due to local recurrence or systemic disease or both, and how to distinguish the low-risk from high-risk patient.

A single abnormal PSA does not necessarily indicate that a biochemical failure has occurred. After prostatectomy, biochemical failure becomes a consideration after the PSA has been measured to be in the 0.2-0.4 range. In general, a low pre-treatment PSA, a lower grade, a lower stage, a longer time from definitive treatment to PSA relapse, and a long PSA doubling time prognosticate a low likelihood for development of systemic metastases and a greater likelihood of local recurrence. **Salvage radiation therapy** (radiotherapy following prostatectomy when a biochemical recurrence is noted) would be an appropriate consideration for biochemical failure due to localized recurrence after prostatectomy, and cryosurgery or androgen deprivation therapy would be an appropriate consideration for biochemical failure due to localized recurrence after radiotherapy.

## *What is Active Surveillance?*

The fundamental challenge of prostate cancer is to predict the biological behavior of the cancer so as to best treat the cancer appropriately—offering curative treatment to those with aggressive cancer, but sparing the morbidity of curative treatment in those who have non-aggressive cancer. The goal of **active surveillance** is to allow men with low risk prostate cancer to avoid radical treatment with its associated morbidity and delay definitive treatment until signs of progression are demonstrated. This involves careful monitoring and a compliant patient.

The ratio of 7:1 of the *lifetime likelihood of diagnosis of prostate cancer* (about 1 in 6 men) to *death from prostate cancer* (about 1 in 40 men) points to the fact that many men with prostate cancer have an indolent cancer. Because of this fact, an alternative strategy to aggressive management of all men with prostate cancer may be active surveillance, a means of careful follow-up with rigorous monitoring and curative intervention should signs of progression develop. Eligibility criteria for active surveillance are the following (Note that these are general guidelines and need to be modified in accordance with patient age and general health—certainly if one has a life expectancy < 10 years, he would be a good candidate for active surveillance, regardless of the following):

- PSA less or equal to 10 ng/ml
- Gleason score 6 or less
- Stage T1c-T2a
- Less than 3 of 12 cores involved with cancer
- Less than 50% of any one core involved

The monitoring schedule is the following:

- PSA and DRE every 3 months for 2 years, then every 6 months
- Biopsy in one year, then every 3 years until age 80 or so (once again, a judgment call)

Of note, a theme in the current urological literature is early repeat biopsy for men on active surveillance, with some centers recommending a repeat biopsy even before considering initiating this management strategy.

One of the best ways of predicting the biological behavior of prostate cancer is by using the *PSA doubling time (PSADT)*. This is defined as the amount of time it takes for the PSA to double. A short PSA doubling time is indicative of an aggressive, rapidly growing tumor, whereas a long PSA doubling time is indicative of an indolent, slow growing tumor. A PSADT of less than 3 years is clearly associated with the potential for progression of prostate cancer.

Curative intervention needs to be instituted if any of the following occurs:

- PSA doubling time is noted to be less than 3 years
- Biopsy reveals grade progression to Gleason 7 or higher
- Biopsy reveals increased prostate cancer volume

Approximately half of men on active surveillance remain free of progression at ten years, and definitive treatment appears to be effective in those with progression. The absence of cancer on repeated prostate biopsy (because the cancer is of such low volume) identifies men who are unlikely to have progressive prostate cancer.

Advantages of Active Surveillance:

- Avoids the morbidity of immediate treatment
- Minimizes over-treatment of indolent prostate cancer

Disadvantages:

- Imprecise criteria for delayed intervention
- Need for frequent and repeated testing and biopsy
- Anxiety of living with untreated prostate cancer
- Delayed treatment may need to be more aggressive with more morbidity
- Delayed treatment may not be curative or as effective as earlier intervention

## *What is a Robotic-Assisted Prostatectomy?*

**Radical prostatectomy** is the surgical removal of the entire prostate and seminal vesicles, with the urethra sutured to the bladder neck to restore the continuity of the lower urinary tract. The three goals are cancer control, preservation of urinary control, and preservation of sexual function.

Historically, open surgical approaches were in vogue for many years—either *retropubic* (via a lower abdominal incision) or *perineal* (via an incision between the scrotum and anus). With evolution of the technique, the laparoscopic approach largely supplanted the open technique, and most recently, use of the robot has further refined the procedure. Whenever possible, a nerve-sparing approach is performed, in order to maximize the potential for satisfactory erectile function after the prostatectomy. The procedure generally entails several hours under anesthesia and typically a one-night stay in the hospital. A catheter typically needs to remain in the bladder for a week or so after the surgery.

Robot-assisted laparoscopic prostatectomy is now the surgical approach of choice for removing a cancerous prostate gland. The *robotic* technology allows a surgeon to sit at a console remote from the patient and perform surgical maneuvers that are reproduced in real time by miniaturized robotic instruments placed via laparoscopic technology. The robotic instruments are introduced into the body through small portals that leave only small scars and cause limited pain after surgery. The surgeon's fingers are inserted into surgical joysticks that provide control of the instruments—the three-dimensional view is optically magnified ten-fold and seven degrees of freedom (each direction a joint can move is a degree of freedom) are provided at the instrument tips. 540 degrees of pivoting provide greater maneuverability than is possible with the human hands or laparoscopic instruments and the robotic arms eliminate even the slightest human hand tremors.

The surgeon's hand movements are translated into precise, real-time movements of the surgical instruments inside the body, allowing the surgeon the benefits of markedly better vision and maneuverability, very refined precision in the dissection of delicate tissue, and facilitation of suturing. The advantages of robotic-assisted prostatectomy over conventional prostatectomy are reduced blood loss, better visualization, precise surgical control, less post-operative pain, shorter hospital stay, and improved outcomes in terms of incontinence and erectile dysfunction.

One of the benefits of prostatectomy is that the removed prostate is scrutinized in its entirety by the pathologist. The pathology report on the removed prostate and seminal vesicles provides important information regarding prognosis. If the report indicates that the cancer is all contained within the prostate capsule with normal margins,

the prognosis is excellent. Adverse features are the following:

- Peri-neural invasion or lympho-vascular invasion (growth of the cancer along the nerve, lymphatic or blood vessel branches)
- Extra-capsular extension (extension of the cancer beyond the prostate capsule)
- Positive surgical margins (cancer at the specimen edge)
- Seminal vesicle invasion (invasion into the seminal vesicles)
- Lymph node metastases (invasion into the lymph nodes)

## *After Radical Prostatectomy*

The PSA after a radical prostatectomy should be zero. If there is a PSA elevation following prostatectomy, it is usually an indication of a *biochemical recurrence* of the prostate cancer, although it can also represent retained benign prostate tissue, in which case the PSA velocity should be expected to be very slow. The most widely accepted definition of a recurrence after radical prostatectomy is a PSA > 0.3.

Important factors governing the likelihood of prostate cancer progression after radical prostatectomy are the *PSA doubling time* (the longer the doubling time, the better the prognosis), the *interval from surgery to the time of biochemical recurrence* (the longer the interval, the better the prognosis) and the *Gleason score* (the lower the score, the better the prognosis). An interval to PSA recurrence of less than 3 years, pathological Gleason score 8-10, and PSA doubling time less than 9 months are poor prognostic features suggesting microscopic metastatic disease.

*Adjuvant radiotherapy*, the use of radiotherapy after radical prostatectomy for T3 disease, has been proven to significantly reduce the risk of PSA recurrence and metastasis and to increase survival.

*Salvage radiotherapy* to the prostatic bed is an effective means of treating locally recurrent disease. It is best given before the PSA gets above 0.5 ng/ml and in the setting of a long PSA doubling time, a longer time interval between surgery and recurrence, and a lower Gleason score. Alternatively, men with recurrent disease with poor prognostic features likely harbor both local and distant recurrence, and are best treated with combined salvage radiotherapy and androgen deprivation therapy.

Without the use of salvage radiotherapy, after a PSA rise is noted, it will typically take about 8 years before metastatic disease occurs and 13 years before death occurs.

#### Advantages of Robotic Prostatectomy:

- A one time procedure that completely removes the cancerous organ and offers an excellent long-term cancer control for many men
- Pelvic lymph node sampling can be performed at the same time, offering staging and prognostic information
- The pathology report on the removed prostate will predict the prognosis
- Provides an excellent means of managing lower urinary tract symptoms
- PSA should be zero after the procedure, so recurrences are easy to detect if PSA is greater than zero
- If it fails to cure the cancer, radiation therapy is available as a back up, potentially curative option
- The major complications, erectile dysfunction and urinary incontinence, are treatable

#### Disadvantages:

- A technically-challenging, major operation that requires anesthesia and a hospital stay and time lost from normal activities
- Potential over-treatment for many low-risk cancers
- Approximately 20-25% will have a PSA recurrence, indicative of failure to cure the cancer
- Possibility of rectal injury, erectile dysfunction, urinary incontinence
- Dry ejaculation
- Penile retraction and shortening
- Possibility of bladder neck contracture—scar tissue where the bladder neck is sewn to the urethra, often necessitating further procedures

## *What is External Beam Radiotherapy (EBRT)?*

Unlike surgery, which removes the diseased prostate gland, the goal of radiotherapy is to kill the prostate cancer cells *in-situ*, where they live. **External beam radiotherapy** uses beams of high-energy gamma rays in order to kill cancer cells. Radiation Oncology is the medical discipline devoted to the use of ionizing radiation in the treatment of patients with cancer. The goal of radiation therapy is to deliver a precise dose of radiation to a defined tumor volume while minimizing the dose and resultant damage to the normal surrounding tissue. A linear accelerator generates and directs beams of gamma rays to the prostate gland, which over several weeks of treatment will kill the cancer cells. Radiotherapy is delivered in such incremental fashion—small doses spread out over a period of weeks—to efficiently kill cancer cells while minimizing damage to normal cells. Each treatment only lasts a few minutes with the total time on the table being about 20 minutes per treatment.

One of the key advantages to radiation over surgery is the ability to treat adjacent tissue beyond the confines of the prostate—this is an important consideration since prostate cancer frequently originates in the peripheral zone of the gland, which is very close to the margin of the prostate. Another advantage of radiation therapy is that surgery is avoided, so there is significantly less impact on important quality of life issues such as continence and erectile function. EBRT treatment courses generally run five days a week for seven to eight weeks and are done on an ambulatory basis.

Radiation therapy, either alone or combined with *brachytherapy* (placement of radioactive seeds within the prostate gland) is a **curative therapy** for early-stage prostate cancer and is used in combination with androgen deprivation therapy (to eliminate testosterone) for patients with high-risk disease. Radiation is also used as **adjuvant therapy** after radical prostatectomy when the pathology report demonstrates a high risk of recurrence or as **salvage therapy** for those patients who develop biochemical recurrence, defined as PSA elevation after surgery. Here the goal is to deliver radiotherapy to the area immediately surrounding where the prostate was, to eradicate any remaining prostate cancer cells. In addition to these curative efforts, radiation is also used as **palliative therapy** to eliminate pain and improve skeletal integrity for those with metastatic disease.

**Conformal radiation therapy (CRT)** has numerous advantages over conventional (2-dimensional) radiotherapy. Utilizing 3-dimensional computer techniques, multiple radiation beams are geometrically shaped to conform to the “beams eye view,” limiting the radiation dose to the prostate gland and eliminating the dose to the surrounding bladder and rectum. Conformal radiation therapy has allowed *dose escalation*—the delivery of higher doses of radiation—with improved cure rates.

**Intensity modulated radiotherapy (IMRT)** is an exponential leap forward compared with CRT, maximizing the treatment to the prostate target while further minimizing dose to the surrounding structures to a degree not possible with conformal therapy. As the name suggests, the intensity of the doses of radiation and the beams are modulated to better target the radiation. The development of dynamic multi-leaf collimators (radiation beam shapers) and inverse planning treatment software allowed for the introduction of IMRT. This computer-controlled modulation of the intensity of the beam across multiple treatment fields is the essence of IMRT and allows for further dose escalation over conformal radiation therapy that further improves cure rates.

**Tomotherapy** is another type of inverse planning IMRT that involves a rotating multi-segmented delivery system in which a linear accelerator and CT scanner are incorporated into one unit. This form of image-guided radiotherapy confirms the position of the prostate gland immediately before each treatment. Before each tomotherapy session, a special CT scan is taken to verify the location of the prostate gland and adjust the patient’s position if necessary to insure that the radiation is directed to the proper area. Because the position of the prostate can shift from day to day, this pre-treatment CT scan is an important improvement in quality assurance. The radiation treatment is delivered in a unique spiral pattern that delivers beamlets of radiation from many angles in a 360-degree radius around the patient. These many angles allow additional degrees of freedom to precisely shape the radiation isodose cloud to conform to the prostate gland without irradiating the bladder or rectum.

**Cyberknife** is a technology originally conceived for treating brain and spinal tumors that has been adapted for prostate cancer. Also known as *stereotactic radiotherapy*, it is a form of high intensity focused radiation that can be completed over the course of 4-5 sessions as opposed to many weeks of standard radiotherapy, and is thus

also known as *hypofractionated radiotherapy*. Its proponents claim that it is more “surgical” than standard radiotherapy, with reduced radiation dosing to the bladder and rectum. Essentially, a computer-controlled robotic arm swivels to shoot dozens of beams of radiation from multiple angles, resulting in high doses that are “sculpted” to the tumor. Although the prospect of a compressed course of radiotherapy in terms of convenience sounds inviting and intriguing, the jury remains out on the cyberknife, with its long term potential for curing prostate cancer undetermined at the present time.

**Proton beam therapy** uses heavy particle beams (protons) generated by linear accelerators or cyclotrons as opposed to standard radiotherapy that uses photons. These beams are difficult to produce and control but possess a unique physical characteristic called “the Bragg peak,” which allows for a sharp distal edge that can reduce the dose to tissue lying a few millimeters from the intended target. Proton therapy is excellent for tumors that are close to the surface and for tumors of the brain and spine.

The first proton center was opened in Loma Linda, California, in 1991, and there are currently about 20 proton facilities in the USA. There is an increasing interest in this modality, but proton therapy remains a contentious issue in the field of radiation oncology.

### Radiation Therapy Survival Rates

Radiation therapy and radical prostatectomy have similar 15-year survival rates with results being best for low risk disease and less effective for intermediate and high risk cancers. Serum PSA is widely accepted as a surrogate endpoint for monitoring the effect of treatment. Unlike surgery, patients successfully treated with radiation therapy still have a prostate gland and are not expected to achieve an undetectable PSA. An acceptable PSA following radiation is a low PSA (<1.0 ng/ml), which typically reaches its lowest point (nadir) 18 months after completion of therapy.

Biochemical failure is defined as 3 consecutive PSA rises over a several month period. In general, the shorter the PSA doubling time, the worse the prognosis.

### Radiation Side Effects

Radiation toxicity is divided into acute and chronic. *Acute toxicity* develops during the 8-week treatment period and consists of urinary frequency and irritation due to inflammation of the urethra (the tube

that drains the bladder through the prostate gland). Patients less commonly develop frequent loose bowel movements due to irritation of the rectum. *Chronic toxicity* develops beyond 3 months after completing radiation therapy. Injury to the microvasculature (small blood vessels) of the organs adjacent to the prostate can cause *proctitis*, with intermittent rectal bleeding in 10% of patients and *cystitis*, with intermittent urinary tract bleeding in a small percentage of men. Erectile dysfunction can occur in 25% of men and often responds to medications including Viagra, Levitra or Cialis.

Advantages of External Radiotherapy:

- Excellent cancer control without major surgery and anesthesia
- Treatment of locally-advanced cancer that extends beyond the confines of the prostate
- Outpatient
- Less impact on quality of life
- Can be done on men with prior prostate surgery

Disadvantages:

- Need for multiple treatment visits to the radiation center
- Technically-challenging procedure requiring sophisticated equipment and multidisciplinary interactions among radiation oncologists, radiologists, medical physicists, and computer planners
- Short-term side effects include fatigue, urinary frequency and frequent bowel movements
- Long-term side effects include the possibility of urinary tract bleeding, rectal bleeding and erectile dysfunction
- If radiation fails, surgery is not usually a viable option because of enhanced complications of surgery after radiation

## *What is Prostate Brachytherapy?*

**Prostate brachytherapy** (also known as interstitial implant or seed implant) is a minimally invasive procedure in which radioactive sources (radioactive seeds) are implanted directly into the prostate gland. These titanium-encapsulated seeds are the size of a grain of rice. *Iodine 125* seeds emit low energy radiation with a half-life of 60 days while *Palladium 103* seeds deliver a higher energy with a half-life of 17 days. After the radiation is “spent”, the seeds that remain

are harmless “shells”. Compared with external beam radiotherapy, prostate brachytherapy is potentially more localized and provides higher radiation doses.

In preparation for the procedure, a volumetric study is performed in which a trans-rectal ultrasound of the prostate gland is done to determine where and how many seeds are to be placed. If the prostate gland is too large (>50cc), it may be beneficial to delay the procedure for several months while medication is given to shrink the prostate gland. Having a prior transurethral resection (TURP or “rotor roter”) procedure is a relative contraindication to brachytherapy.

The procedure is performed under anesthesia, usually in an ambulatory surgical center under collaboration of the urologist and radiation oncologist. The patient is placed on his back with his legs up in stirrups with the scrotum taped up out of the way. Needles are placed through the perineum (the skin between the scrotum and anus) under precise ultrasound control through a template positioned against the skin. Once the needles have been placed, the radioactive seeds are injected in predetermined positions throughout the prostate gland. The seeds remain in the prostate and emit radioactivity to the cancer cells over several months. After the procedure, a pelvic CT scan is obtained to check the position of the seeds in the prostate gland and to calculate the delivered dose. A urinary catheter is usually left in overnight to drain the bladder.

Brachytherapy may have minor side effects such as urinary frequency, a weakened urinary stream and burning during urination or ejaculation. These symptoms are usually treated with medications to provide symptomatic relief, and typically resolve within several weeks to several months. The chances of developing erectile dysfunction or incontinence with brachytherapy are less compared to other treatments.

Many patients are treated with a combination of androgen deprivation (to eliminate testosterone) and external radiotherapy in conjunction with brachytherapy. Androgen deprivation will not only shrink the prostate gland but it will also sensitize the prostate gland to increase the effectiveness of brachytherapy. The external radiation not only increases the radiation dose but also provides treatment for disease beyond the immediate confines of the prostate.

A transient PSA elevation known as a “PSA bounce” commonly occurs between 12 and 36 months after seed implant. This phenomenon is thought to be due to inflammation of benign tissue, is commonly seen in the younger population, and occurs more often when Iodine 125 seeds are used.

Advantages of Prostate Brachytherapy:

- Excellent cancer control with long-term cure rates equivalent to surgery while avoiding radical surgery
- Accurate targeting, resulting in decreased radiation to adjacent tissues
- Outpatient, short procedure, with rapid return to normal function
- Minimal risk of long-term urinary, rectal, or sexual side effects

Disadvantages:

- Need for anesthesia
- Patients with larger prostates will need androgen deprivation therapy to shrink the prostate down to a treatable size
- Usually contraindicated in those who have undergone transurethral resection of the prostate
- Technically challenging with results operator-dependent
- Short-term urinary, rectal and sexual side effects
- Radiation precautions – keeping a 6 foot distance from infants, young children, and pregnant women – need to be taken for 6 weeks or so
- If brachytherapy fails, surgery is generally not a viable option

**High dose rate brachytherapy (HDR)** is another form of prostate brachytherapy in which flexible plastic needles are temporarily placed through the perineum (skin between the testicles and the rectum) and are used as a vehicle through which an *Iridium-192* wire is advanced into the prostate gland. A computer-controlled system calculates how long the wire stays in each dwell position in the needles, which determines the delivered dose. Patients receive 3 fractions of high dose radiotherapy over a 24-hour hospital stay. No radioactive sources are left in the prostate and no special radiation precautions are necessary. HDR is typically reserved for those patients with high-risk disease.

## *What is High-Intensity Focused Ultrasound (HIFU)?*

**High-Intensity Focused Ultrasound** is a procedure that has been available in Europe for a number of years and is considered to be a minimally invasive means of treating prostate cancer. This procedure, which is performed under anesthesia and takes between 1-4 hours, is done by placing a special probe in the rectum that generates high-intensity ultrasound waves. These HIFU waves are delivered to the target area within the prostate to ablate the cancer by heating the prostate to such an extent that destruction of prostate tissue occurs, without damaging tissue in the path of the ultrasound beam. 1-4 overlapping target areas are defined and treated. If necessary, transurethral resection of the prostate (a procedure to create a channel through the prostate gland), is performed immediately before the HIFU to reduce the risk of prolonged urinary retention and reduce the size of the prostate. Obstruction due to scarring or necrosis of prostatic tissue is the most common adverse effect. Although this procedure has great potential, the jury is still not out with regards to its long-term success. Unlike radical prostatectomy and radiotherapy, HIFU is considered by many to be an “emerging” therapy.

### Advantages of HIFU:

- Outpatient procedure with minimal time lost from normal activities
- Low morbidity
- Relatively non-invasive
- Can be repeated if necessary

### Disadvantages:

- Heat can damage erectile nerves
- Difficulty in ablating the entire prostate, especially in a large prostate
- Difficulty in treating anterior prostate cancers
- Sparse data on long-term results
- Need for prolonged catheterization to drain the bladder

## *What is Cryosurgery?*

**Cryosurgery**, a.k.a. **Cryotherapy** or **Cryoablation** is a procedure in which the prostate cancer is ablated by freezing it, literally to *death*. In essence, subjecting the prostate gland to freezing creates frostbite, which destroys it. The freezing results in direct cellular toxicity in which the ice crystals disrupt the prostate cell membranes, and vascular toxicity in which the blood supply to the cells is injured.

Freezing is achieved using pressurized argon gas circulating through hollow needles called *cryoprobes* that are positioned strategically within the prostate gland (in similar fashion to the way needles are placed into the prostate for brachytherapy radiation) using trans-rectal ultrasound guidance and a perineal template. The procedure is done under anesthesia with the legs up in stirrups. The urethra is kept warm with a warming catheter that uses helium gas. Thermocouples (sophisticated thermometers) are placed to precisely monitor temperatures. A tissue temperature of  $-40$  to  $-50$  degrees Centigrade is achieved. Under most circumstances, the prostate is subjected to two cycles of freezing and thawing. The procedure can be done on an outpatient or one-night-stay basis, and the patient is sent home with a catheter.

*Primary cryosurgery* is suitable for stage T1c-T3 disease of any grade in men who are not sexually functional or those not interested in being sexually active. If the prostate is large, androgen deprivation therapy is useful to reduce the volume and allow for more effective results. Freezing extending beyond the capsule of the prostate can potentially eradicate extra-capsular disease. *Salvage cryosurgery* is used for recurrent disease following radiation therapy.

Although the current technology is third generation, cryosurgery is still considered by many to be an “emerging” therapy and not quite in the same league as radical prostatectomy and radiotherapy. It is unquestionably much improved over previous iterations, but there are still potentially serious morbidities that can result. If the freezing extends beyond the intended treatment zone, damage to the urethra and rectum can occur, including *urethral sloughing* (passage of dead tissue through the urethra) and *recto-urethral fistula* (an abnormal connection between the rectum and the urethra).

Advantages of Cryosurgery:

- The treated lesion (“ice ball”) is visible on ultrasonography
- Can be used for focal ablation of one lobe of the prostate under the circumstance that the prostate cancer is clearly localized to one side
- Can be repeated, if necessary

Disadvantages:

- Tissue damage to adjacent structures
- Difficulty in treating anterior prostate cancers
- Lack of data on long-term follow up
- Incontinence
- Erectile dysfunction

## *What is Androgen Deprivation Therapy (ADT)?*

**Androgen deprivation therapy (ADT) or androgen suppression therapy** is also referred to as **hormone therapy**. The goal is to reduce levels of the male hormones called androgens. The main androgens are testosterone and dihydrotestosterone (DHT). Androgens, 90% of which are produced in the testicles, stimulate both benign and malignant prostate growth. Lowering androgen levels often makes prostate cancers shrink or grow more slowly. However, hormone therapy does not cure prostate cancer. Although never curative, many patients with prostate cancer do experience long-term remissions. Although ADT delays clinical and biochemical disease progression, the effects on survival are less clear. Because of side effects and what can be construed as acceleration of the aging process, ADT should only be used when clearly indicated and avoided when possible.

Hormone therapy may be used in the following situations:

- As a means of temporizing because of the need to defer definitive treatment
- If one is unable to tolerate surgery or radiation because of compromised health or advanced age, but still desires to be treated

- In conjunction with radiation therapy since radiation and ADT have a synergistic effect and the combination inhibits cancer progression
- Prior to surgery or radiation to shrink the cancer and to make other treatments more effective (although ADT reduces the incidence of positive surgical margins after prostatectomy, it has no effect on PSA progression)
- To treat surgery or radiation failures
- To treat metastatic disease

There are several types of hormone therapy used to treat prostate cancer.

**Orchiectomy (surgical castration):** In this operation, the urologist removes the testicles, where the majority of the androgens, mostly testosterone, are made. With this source removed, most prostate cancers stop growing or shrink for a time. This is done as a simple outpatient procedure. It is the least expensive and simplest way to reduce androgen levels in the body. But unlike other methods of lowering androgen levels, it is permanent, and many men—understandably so—do not want to have their testicles removed. Most men who have this operation have reduced or absent libido (sexual desire). Some men also experience:

- hot flashes (these may go away with time)
- erectile dysfunction
- breast tenderness and growth of breast tissue
- osteoporosis (bone thinning), which can lead to broken bones
- anemia (low red blood cell counts)
- decreased mental acuity
- loss of muscle mass
- increase in body fat
- weight gain
- fatigue
- weakness
- altered lipid profiles: increased cholesterol and decrease in HDL (“good”) cholesterol

- increased incidence of type 2 diabetes and coronary disease
- depression

**Luteinizing hormone-releasing hormone (LHRH) analogs:** LHRH analogs (also called LHRH agonists) lower testosterone levels just as well as orchiectomy by lowering the levels of androgens (mainly testosterone) made by the testicles.

LHRH analogs are injected or placed as small implants under the skin. They are given either monthly or every 3, 4, 6, or 12 months. The LHRH analogs available in the United States include leuprolide (Lupron, Viadur, Eligard), goserelin (Zoladex), and triptorelin (Trelstar). Possible side effects of LHRH analogs such as hot flashes, osteoporosis, and others are similar to those of orchiectomy (see p. 39).

When LHRH analogs are first given, testosterone production increases briefly before falling to very low levels. This effect is called the *flare or surge phenomenon*. Men whose cancer has spread to the bones may experience bone pain. If the cancer has spread to the spine, even a short-term increase in cancer growth could compress the spinal cord and cause pain or paralysis. Flare can be avoided by giving drugs called anti-androgens for a few weeks when starting treatment with LHRH analogs. (For more on anti-androgens, see below.)

**Luteinizing hormone-releasing hormone (LHRH) antagonists:** Two newer drugs, Abarelix and Degarelix, are LHRH receptor antagonists. They are thought to work like LHRH agonists, but appear to reduce testosterone levels more rapidly and do not cause the testosterone surge like the LHRH agonists do. The possible side effects are similar to those with orchiectomy (see page 39) or LHRH agonists.

**Anti-androgens:** Anti-androgens block the body's ability to use any androgens. Even after orchiectomy or during treatment with LHRH analogs, a small amount of androgens is still made by the *adrenal glands*, located above the kidneys. Drugs of this type, such as flutamide (Eulexin), bicalutamide (Casodex), and nilutamide (Nilandron), are taken daily as pills. Anti-androgens are only very rarely used by themselves, more often used in the setting in which treatment with orchiectomy or an LHRH analog is no longer working by itself. Anti-androgen treatment may be combined with

orchiectomy or LHRH analogs as first-line hormone therapy. This is called *combined androgen blockade (CAB)*, and functions to block adrenal as well as testicular androgens. There is still some debate as to whether CAB is more effective in this setting than using orchiectomy or an LHRH analog alone. If there is a survival benefit, it appears to be small, in the range of 3% after 5 years of treatment. *Side effects* of anti-androgens in patients already being treated by orchiectomy or with LHRH agonists are usually not serious. Diarrhea is the major side effect, although nausea, liver problems, and fatigue can also occur.

If hormone therapy including an anti-androgen stops working, some men seem to benefit for a short time from simply stopping the anti-androgen—this is known as the *withdrawal phenomenon*. Approximately 15–30% of patients who have a rising PSA on combined androgen blockade (ADT including an anti-androgen) will experience a 50% reduction in PSA that lasts for 3.5-5 months after withdrawal of the anti-androgen.

**Other androgen-suppressing drugs:** Estrogens were once the main alternative to orchiectomy for men with advanced prostate cancer. Because of their possible side effects (including blood clots and breast enlargement), estrogens have been largely replaced by LHRH analogs and anti-androgens. Ketoconazole (Nizoral), initially used for treating fungal infections, blocks production of androgens and is occasionally used.

**Current Controversies in Hormone Therapy:** There are many hormone therapy issues that there is no clear consensus on:

**Early vs. delayed treatment:** Some urologists feel that ADT works better if it is started as soon as possible if the cancer has reached an advanced stage (for example, when it has spread to lymph nodes), if it is high stage (T3) or has a high Gleason score, or if the PSA starts rising after initial therapy, even though the patient feels well. Alternatively, other urologists feel that because of the side effects and the probability that the cancer could become resistant to therapy sooner, treatment should not be started until symptoms from the disease appear.

**Intermittent vs. continuous hormone therapy:** Most prostate cancers treated with hormone therapy become *resistant* to this treatment after a number of years, a condition referred to as *Hormone Resistant Prostate Cancer (HRPC)*. Some urologists believe that constant androgen suppression may not be needed, so they advise intermittent (on-again, off-again) treatment. Androgen suppression is stopped once the blood PSA level drops to a very low level and when the PSA level begins to rise, the ADT is re-started. It is premature to state whether this new approach is better or worse than continuous hormonal therapy; however, one advantage of intermittent treatment is minimizing the side effects of ADT.

**Combined androgen blockade (CAB):** See above discussion. Some urologists treat patients with both androgen deprivation (orchiectomy or an LHRH agonist) and an anti-androgen. However, most are not convinced that combined therapy is superior to one drug alone.

## *How is Hormone-Resistant Prostate Cancer (HRPC) Managed?*

When prostate cancer grows resistant to ADT and *hormone-independent* prostate cancer cells proliferate, *chemotherapy* becomes a consideration. Chemotherapy is a *systemic* (as opposed to *local*) treatment that can control the progressive growth and destroy prostate cancer cells that have become resistant to ADT.

Prostate cancer chemotherapy is usually employed as a *salvage treatment* for HRPC or for advanced prostate cancer with metastatic disease. Chemotherapy is most effective for rapidly dividing cells; since many prostate cancers grow relatively slowly, chemotherapy is not usually a primary form of treatment as is surgery or radiation. All rapidly dividing cells are affected by chemotherapy—hair, skin, gastro-intestinal tract, testes, bone marrow—the adverse effects on these systems can outweigh the benefits in the treatment of early prostate cancer, but chemotherapy can be beneficial in terms of treating pain and extending life under certain circumstances.

When prostate cancer progresses despite androgen deprivation therapy, it can be clinically asymptomatic causing only a rising PSA, or it can cause symptoms, most commonly bone pain since prostate cancer has a predilection to involve the skeleton. The initial approach is always to ensure that *castrate* levels of testosterone

(less than 50 ng/ml) have been achieved. If an anti-androgen has been used, it should be discontinued to test if there will be a salutary response to its withdrawal. If an anti-androgen has not been tried, it is worthwhile at this juncture to utilize it. If castrate levels of testosterone have not been achieved with combined androgen blockade, second-line hormonal therapy should be considered—either *megesterol* or adrenal androgen inhibitors such as *aminoglutethamide* or *ketoconazole*.

If second-line hormonal therapy fails to stem the progression of prostate cancer, chemotherapy can be of utility. Medical Oncology is the medical discipline devoted to the use of cytotoxic (cell-killing) medications to treat cancer. The basic principle of chemotherapy is to use such medications, either alone or in combination, to stop malignant cells from dividing and thus growing and spreading.

The current standard chemotherapy treatment for HRPC is *docetaxel* (Taxotere), a member of the taxol family, derived from bark of the Pacific Yew tree. It was approved by the FDA in 2004 and has been shown to increase survival, alleviate pain, and increase quality of life. However, it can suppress production of blood cells and platelets and cause fatigue, edema (swelling), neurological toxicity and changes in liver function. The standard treatment prior to the docetaxel era was the combination of *mitoxantrone* (Novantrone) plus *prednisone*. There are numerous ongoing clinical trials that are testing the safety and efficacy of a myriad of different chemotherapeutic agents in terms of treating HRPC.

## *What is Palliative Management?*

Palliative therapy is supportive care that involves management of pain from bony metastases as well as management of urinary tract obstruction. The goal of palliation is improvement in the symptoms of prostate cancer without curing the disease.

### **Localized bone pain**

Prostate cancer bone metastases are collections of prostate cancer cells that have taken residence within the bones, as distinguished from a primary bone cancer. Patients with isolated bony metastases that are symptomatic typically have unrelenting, well-localized pain. The pain may be effectively treated with localized radiotherapy to kill the cancer cells within the bones. This treatment is often referred to as *spot radiation*. A pathological fracture is defined as

a broken bone occurring as a result of weakness from the normal cells having been replaced with cancer cells and not on the basis of trauma to the bone. If a pathological fracture from the prostate cancer involves a weight-bearing bone, orthopedic surgery (in addition to radiation) may be necessary to stabilize the bone. The most common pathological fracture from prostate cancer occurs in the hip region.

*Biphosphonates* such as *Zoledronic acid* are important in the management of bony metastases. This potent, intravenously administered medication, is used in conjunction with calcium and vitamin D to help to re-mineralize bone and decrease the chance of *adverse skeletal events* (pathological fractures, vertebral collapse and spinal cord compression). Zoledronic acid can cause fatigue, muscle aches, fever, anemia, occasional increase in serum creatinine (blood marker for kidney function), and rare jaw osteonecrosis (loss of bone integrity of the jawbone).

### **Diffuse bone pain**

For patients with extensive bony metastases that are symptomatic, systemic radionuclide therapy using radiopharmaceuticals may be helpful. *Strontium-89* (Megastron) is administered intravenously and is quickly taken up in the mineral matrix of bone. Preferential accumulation occurs in metastatic bone deposits, where the radiopharmaceutical releases radiation that kills the cancer cells. Elimination of Strontium occurs through the kidneys, so careful disposal of urine is required for 7 to 10 days after treatment.

### **Spinal cord compression**

Spinal cord compression is a serious emergency for patients with metastatic prostate cancer. The vertebrae are stacked atop one another and when weakened by prostate cancer, can collapse, compressing the spinal cord and nerves. Additionally, the nerves or spinal cord can be pinched by the presence of metastatic disease even in the absence of vertebral collapse.

Prostate cancer patients with back pain should be evaluated for the presence of vertebral metastatic disease that can lead to compression of the spinal cord and, in addition to severe back pain, can cause leg weakness, altered sensation, and bladder and bowel symptoms. This is an emergency situation that needs rapid evaluation with a MRI of the spine and treatment with high-dosage intravenous steroids followed by radiotherapy to the involved vertebra. Neurosurgical intervention may be necessary if there is

progression during radiation therapy or if there is a recurrence after radiation therapy. If ADT has not been used previously, immediate hormonal therapy should be instituted, medically with ketoconazole or surgically with orchiectomy.

### **Urinary tract obstruction**

Lower urinary tract obstruction can occur as the prostate cancer growth occludes the bladder outlet. This sometimes will need to be treated with the surgical creation of a channel through the obstruction, in order to restore normal urinating.

Upper urinary tract obstruction can occur if the ureters are compressed by local infiltration of the prostate cancer directly into the bladder base or by pathologically enlarged lymph nodes. This can be managed with *ureteral stenting* (placement of small catheters within the ureters that alleviate the obstruction) or *percutaneous nephrostomy tubes* (placement of small catheters directly into the kidneys from the flank to alleviate the obstruction).

## *Future Directions*

Aggressive efforts and inroads are being made in terms of prevention, detection, diagnosis, research, and novel treatments of prostate cancer. Perhaps the most profound and significant finding in the prostate cancer domain was the National Cancer Institute study that proved that Finasteride can successfully prevent prostate cancer.

Focal therapy, defined as treatment directed at only the cancerous part of the prostate gland, has future potential, but remains controversial because of the multi-focal nature of prostate cancer. In select patients, it can offer a compromise between active surveillance and treatment of the entire prostate gland. Cryoablation and HIFU are the primary modalities that can be used on a focal basis.

There are an abundance of new medications under investigation in clinical trials. As opposed to chemotherapy medications that are cytotoxic and do not distinguish between normal cells and malignant cells, *targeted therapies* designed to target only the cancer cells, are sources of investigation. There are current clinical trials of medications that inhibit the activity of growth factor receptors, those that interfere with the blood supply to cancer cells, and those that stimulate the immune system to fight off prostate cancer cells. *Therapeutic vaccines* that train the body's immune system to attack cancer cells including *Provenge* and *GVAX* are undergoing extensive clinical testing.

The future of improved treatment options for prostate cancer, even metastatic prostate cancer, remains optimistic. Advances in the field of molecular genetics, the branch of genetics concerned with the structure and activity of genetic material at the molecular level, will play a pivotal role. There will come a time, in the not-too-distant future, when we will be able to obtain a molecular “blueprint” of any given tumor. It is believed that this information will greatly aid in making immense strides in fighting—and curing—this disease.

*“The signature of the tumor will allow us to fully assess the genetic nature of the enemy, how aggressive it is, what its metastatic intentions are, what it is sensitive to, and how best to attack it. At the same time, we will be armed with a whole battery of potent oral agents capable of targeting specific signaling pathways in the tumor.”*

Dr. Arie Belldegrun (UCLA School of Medicine)

## *Additional Resources*

**American Cancer Society:** [www.cancer.org](http://www.cancer.org)

**American Urological Association Foundation:** [www.auafoundation.org](http://www.auafoundation.org)

**Cancer Care:** [www.cancercare.org](http://www.cancercare.org)

**National Cancer Institute:** [www.cancer.gov](http://www.cancer.gov)

**National Prostate Cancer Coalition:** [www.pcacoalition.org](http://www.pcacoalition.org)

**Prostate Cancer Foundation:** [www.prostatecancerfoundation.org](http://www.prostatecancerfoundation.org)

**Prostate Cancer Research and Education Foundation:**  
[www.pcref.org](http://www.pcref.org)

**Us TOO Prostate Cancer Education and Support Network:**  
[www.ustoo.org](http://www.ustoo.org)

## *About the Author*

Dr. Andrew Siegel is an honor graduate from the Chicago Medical School, Chicago, Illinois. After completing his general surgical training at North Shore University Hospital, Manhasset, New York, he trained in urology at the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. He went on to complete an additional year of fellowship training at the UCLA School of Medicine, Los Angeles, California. He joined Bergen Urological Associates and the staff of Hackensack University Medical Center in 1988.

Dr. Siegel is a board-certified urological surgeon who is a member of numerous professional medical associations and societies. He has authored chapters in urology textbooks and has published a multitude of articles in professional journals. He has presented papers at medical meetings both nationally and internationally. He serves as a Clinical Assistant Professor of Urology at the University of Medicine and Dentistry of New Jersey and is actively involved in the training of urology residents.

One of Dr. Siegel's key interests lies in patient education and, in this regard, he has written numerous booklets and monographs on a great deal of urological subjects and has created a number of educational videos that are available on the Internet. He has a profound passion for and is an ardent advocate of maintaining health and fitness through the practice of nutritional conscientiousness, exercise and intelligent lifestyle choices. Dr. Siegel is the author of the 2008 book *Finding Your Own Fountain of Youth—The Essential Guide to Maximizing Health, Wellness, Fitness & Longevity*. For more information about his book, including excerpts and purchasing information, please go to the following website: [www.findingyourownfountainofyouth.com](http://www.findingyourownfountainofyouth.com)



